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Archives OF NEUROLOGY AND PSYCHIATRY

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Wallace B. Hamby

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Amyotrophic Lateral Sclerosis in the Mariana Islands
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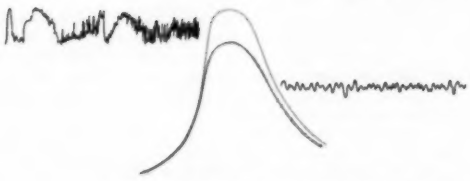

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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The Surgical Treatment of Intracranial Aneurysms

Results in Angiographically Located Lesions

WALLACE B. HAMBY, M.D., Buffalo

In previous reports from this hospital no attempt has been made to evaluate the effects on patients of various methods used in treating intracranial aneurysms. Statistics including the entire group of 163 verified aneurysms are no longer of value in determining the effects of surgical therapy. The present report concerns only the cases in which nonfistulous aneurysms, localized by angiography, were attacked in a definitive manner.

MATERIAL

This series (Table 1) includes 69 cases, in which 51 patients were treated, with a mortality rate of 21.5%, and 18 were untreated, with a mortality rate of 61%. The total fatality rate was 32%.

Subarachnoid Hemorrhage and Time of Operation

Aneurysms had ruptured, producing subarachnoid hemorrhage in 43 of the 51 patients treated and in 15 of the 18 untreated. As others also have reported, the risk of operation in these cases is greatest in the first week after hemorrhage. Of seven cases, operation in the first week after either primary or secondary hemorrhage was followed by death in five (72%). Operation in the second week resulted in two fatalities in six cases (33%). In the third week 2 of 12 patients died (17%). Four operations were done in the fourth week, with no deaths. Two fatalities occurred in 14 patients whose aneurysms had bled more than four weeks earlier (15%). If the figures are arranged a little differently, it is evident that 7 patients (53%) died among 13 operated upon in the first two weeks following hemorrhage, while of those operated on thereafter only 4 of 30 (13%) died. There were no surgical fatalities in the series of eight patients whose aneurysms had not bled. It is obvious that in the evaluation of statistical reports on the results of the surgical treatment of intracranial aneurysms, the time of operation after hemorrhage is of the utmost importance.

Analysis of the four fatalities following surgery done after the second week disclosed a variety of surgical mishaps. Some of these might reasonably be considered avoidable with presently available aids in treatment.

Patient 51 was operated upon in 1948, at an interval of 17 days following subarachnoid hemorrhage from a large aneurysm of the anterior communicating artery. The lesion ruptured afresh during exposure. In an attempt to control hemorrhage without benefit of hypotension, clips inadvertently occluded both anterior cerebral arteries. The patient died of infarcted frontal lobes and a pontine hemorrhage.

Patient 70 also was operated upon in 1948, at an interval of 33 days following hemorrhage from a tiny aneurysm in the angle between the right an-

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From the University of Buffalo School of Medicine and the Buffalo General Hospital.

terior cerebral and communicating arteries. This lesion also ruptured during exposure. In an attempt to avoid clipping uninvolved vessels at the communication, a special temporary clip was placed with great care on the right internal carotid artery. The aneurysm then was controlled with silver clips, and the temporary clip was removed from the carotid. The patient died of thrombosis of the internal carotid, extending from the site of the temporary clip through the middle cerebral artery.

Patient 125 was operated upon in 1953, six days after subarachnoid hemorrhage from an aneurysm of the left internal carotid artery at the junction of the posterior communicating artery. This 39-year-old woman had cerebral vascular disease also. From angiographic evidence and because she had tolerated occlusion of the left internal carotid artery with a Poppen clamp for two days, collateral circulation was considered adequate. At operation, with hexamethonium-induced hypotension, the neck of the aneurysm was found to be too wide for closure with the clips available. The lesion and its parent carotid trunk were occluded with several clips. The patient died with an infarcted left hemisphere. It is believed that collateral flow from the posterior communicating artery had protected her circulation prior to operation.

Patient 138 was operated upon 30 days after hemorrhage from a subchiasmal aneurysm of the internal carotid artery. The lesion was trapped with clips. He recovered promptly but died on the fifth day, of unrecognized subdural empyema.

Forms of Treatment

Of the 51 cases (Table 1), treatment of 12 consisted of cervical carotid ligation alone, with a fatality rate of 25%. One of the original survivors of this group (#90) died two years later, of recurrent hemorrhage. Aneurysms were excluded from the circulation by trapping the lesion between proximal and distal occlusions of the parent trunk in 18 cases, with a fatality rate of 22%. In 10 cases the trap consisted of cervical ligation of the common or internal carotid below the lesion and a silver clip above. The fatality rate was 10%. In eight cases the trapping was accomplished by clipping the carotid on each side of the aneurysm, usually when the aneurysmal neck was considered unsuitable for occlusion at exploration, or when attempt at its occlusion resulted in hemorrhage otherwise uncontrollable. The fatality rate in this group was higher, 37.5%, as might be expected of a modality of treatment employed in especially difficult cases.

We have concluded that, when feasible, the ideal treatment of an intracranial aneurysm consists of occlusion of its neck, the cerebral circulation otherwise being left

Table 1.—*Summary and Results of Management of Sixty-Nine Patients with Angiographically Demonstrated Intracranial Aneurysms*

				Deaths	
Total no. of patients	69			22 (32%)	
Untreated patients	18			11 (61%)*	
Treated patients	51			11 (21.5%)	
Cervical ligation only		12		3 (25%)	
Subclinoid carotid		1		0	
Supraclinoid carotid		11		3 (27%)†	
Trapped		18		4 (22%)	
With cervical ligation		10		1 (10%)	
Subclinoid carotid			1	0	
Supraclinoid carotid			9	1	
Intracranial only		8		3 (37.5%)	
Supraclinoid carotid			3	0	
Carotid bifurcation			1	0	
Anterior cerebral			3	2	
Anterior communicating			1	1	
Occlusion of aneurysm neck		20		4 (20%)	
Supraclinoid carotid		12		2 (17½)	
Carotid bifurcation		3		1	
Anterior communicating		2		0	
Anterior cerebral		1		0	
Middle cerebral		2		1	
Reinforcement only	1			0	
Middle cerebral		1		0	
	51	51		11	11

* Two patients (Nos. 53 and 161) died within six weeks of recurrent hemorrhage.
† One patient (No. 90) died later of recurrent subarachnoid hemorrhage.

intact. This is our present goal in treating all cases, and other methods constitute forced retreats from this attempt. The aneurysmal neck may be occluded by metallic clips or by ligature; clips have been used more frequently in this series. Twenty patients have been treated by this method, with a fatality rate of 20%. For supraclinoid lesions, this therapy was slightly safer in series of comparable size than was carotid ligation alone, with the added advantage that was not considered possible. The entire complex having been completely isolated, it was covered carefully with thinly hammered sheets of muscle and then with a thin sheet of Cottonoid. Progress for three years has been satisfactory from the aneurysmal standpoint, but contralateral convulsions, existing since hemorrhage, have continued unabated.

Table 3 details the present status of the 51 patients whose aneurysms were treated surgically.

TABLE 2.—*Location of Aneurysms in This Series of Sixty-Nine Patients*

Artery	Treated		Untreated		Total
	Total	Died	Total	Died	
Subclinoid carotid	2	0	1	1 (100%)	3
Supraclinoid carotid	35	6 (17%)*	2	1 (50%)	37
Carotid bifurcation	4	1 (25%)	..	..	4
Anterior cerebral	4	2 (50%)	3	3 (100%)	7
Anterior communicating	3	1 (33%)	5	3 (60%)†	8
Middle cerebral	3	1 (33%)	5	2 (40%)‡	8
Multiple	..	..	2	1 (50%)	2
	51	11 (21.5%)	18	11 (61%)	69

*Another patient (No. 90) died two years later of recurrent subarachnoid hemorrhage.
† Another patient (No. 161) died two weeks later of subarachnoid hemorrhage.
‡ Another patient (No. 53) died six weeks later of subarachnoid hemorrhage.

TABLE 3.—*Present Status of Patients with Surgically Treated Aneurysms*

	Carotid Ligation	Trapping Operations	Occlusion Aneurysm Neck	Reinforcement	Total
Total no. of cases	12	18	20	1	51
Surgical fatality	3 (25%)	4 (22%)	4 (20%)	..	11 (21.5%)
Survivors	9	14	16	1	40
Status unknown	1	..	..	..	1
Well	2	5	9	..	16
Working, with mild neurologic deficits	3	6	3	..	12
Considerable neurologic deficit	1	2	3	1	7
Invalid	..	1	1	..	2
Subsequent death	1 (hemorrhage) 1 (unrelated)	1 (unrelated)	..	..	3

the circulation was preserved intact. Table 1 discloses that lesions of the supraclinoid portion of the carotid have been most frequently treated so, but these have been our most commonly encountered ones, 35 of 51 (Table 2).

In only one case was reinforcement of the aneurysmal wall selected as the sole treatment. A 12 mm. aneurysm of the right middle cerebral artery was found to have two of the major branches of the vessel so firmly embedded in its wall that their separation

UNTREATED CASES

The group classified here as "untreated" requires some explanation and analysis. Of these 18 patients, 11 (61%) died in the hospital and 2 more died later at home of hemorrhage, within six weeks, raising the fatality rate to 72%. The physical condition of eight patients was so poor that operation was never considered warranted, and seven of them died.

The one patient of the eight who lived (#44) is illustrative of this group. Thirteen days after her

second bout of subarachnoid hemorrhage, angiography revealed aneurysm of the right middle cerebral artery. She remained irrational and disoriented, with left hemiplegia. Her mental condition gradually improved, but the hemiplegia persisted. The family refused surgical therapy and took her home, against advice, two weeks later. We have not been able to get in contact with the family since.

Another patient (# 134), with long-standing mitral aortic insufficiency, had active bacterial endocarditis on admission. Angiography seven days after an attack of subarachnoid hemorrhage disclosed a left supraclinoid aneurysm. She died the following day.

Six days after an attack of subarachnoid hemorrhage, angiography in Patient 86 showed an aneurysm of the right anterior cerebral artery. She was hemiplegic on the following day and died on the next. Permission for autopsy was not granted.

Another, 43-year-old, patient (# 144) was severely hypertensive. Angiography seven days after a second bout of subarachnoid hemorrhage showed an aneurysm of the anterior communicating artery. She was treated medically for hypertension, but she died suddenly two weeks after the angiography. Autopsy showed a fresh hemorrhage to have ruptured through the left frontal lobe into the ventricle.

Angiograms of Patient 106 revealed four aneurysms, two on the right middle cerebral artery, one on the left middle cerebral artery, and one on the left anterior cerebral artery. Clinical findings did not indicate the one responsible for the hemorrhage; so surgery was not advised. The patient recovered and is alive and working at present, four years after hemorrhage.

In one case (# 140) a 52-year-old, hypertensive patient was subjected to angiography four days after hemorrhage; an aneurysm of the left middle cerebral artery was disclosed. Twelve days later, carotid pressure studies showed that occlusion of the common carotid artery reduced the internal carotid pressure to 25% of its original level. Treatment was deferred. The patient was hemiplegic the next day and died the following day. Autopsy showed the left middle cerebral artery to be thrombosed. The aneurysm had not leaked again and would have been controlled easily with a clip on its neck. At present we should attack such a lesion directly.

A 59-year-old woman (# 53) had an asymptomatic, partly calcified intrasellar tumor and an aneurysm of the left middle cerebral artery. Since the aneurysm had not bled, we allowed her to return home untreated. She died of hemorrhage six weeks later.

Patient 161, a vigorous 40-year-old man, had a subarachnoid hemorrhage, from which he recovered in two weeks. Six weeks after the first attack came another, which produced no neurologic deficits. An angiogram obtained nine days later disclosed a large (13 mm.) aneurysm on the anterior communicating artery. The aneurysm, as well as both distal anterior cerebral arteries, filled equally well from each carotid injection. These phenomena persuaded us that successful occlusion of the aneurysm carried a considerable risk to the anterior cerebral circulation. The patient and his family being unwilling to assume the hazard, he was treated conservatively for four weeks and was discharged. Three weeks later he suddenly had a third, and fatal hemorrhage.

Another patient (# 87) was subjected to angiography in investigating the cause of headache. A left middle cerebral aneurysm was found, but was not treated. She remains well at present, five and a half years after the discovery of the aneurysm, which has never ruptured.

Two patients included in this group had metal bands applied to the carotid artery. These were necessarily removed; hence the aneurysms actually were untreated.

In Patient 95, angiography five days after subarachnoid hemorrhage showed a left supraclinoid carotid aneurysm. The left internal carotid artery was closed partially by a tantalum band. No complications developed, and seven days later the band was closed completely. On the following morning aphasia and right hemiplegia had developed. The band was removed. Symptoms gradually cleared, and the patient recovered. She would take no additional chances with suggested therapy and five years later is alive and happy, with mild hemiparesis and mild aphasia.

It may be argued by some that subsequent events indicate that even the temporary occlusion of the carotid trunks favorably influenced these aneurysms. Since we have not been able to repeat the angiography, we prefer to consider these people untreated.

In addition, we have done craniotomies on three patients (#56, #58, #132), evacuating hematomas. Since we failed to find aneurysms that had been shown on angiograms, nothing actually was done to the lesions. These fatal cases also were classified as untreated.

Present Method of Treatment

It is our present conviction that treatment of sacular intracranial aneurysms should be directed toward the occlusion of the aneurysm and preservation of the existing arterial

circulation. Angiography is done as soon after the patient's admission as his condition permits. A comatose, hemiplegic patient is left alone until he improves, at least moderately. Thereafter he is kept under careful observation, in an attempt to await subsidence of the spinal fluid pressure to a level below 200 mm. of water.

With use of local analgesia, the ipsilateral common carotid artery is exposed and is closed with a small Blalock-Poppen clamp sufficiently to obliterate the superficial temporal pulse. If no symptoms develop in 15 minutes, the wound is closed around the shaft of the clamp and the neck is dressed. The patient is kept under constant observation for the next 24 hours. Should signs of cerebral ischemia develop, the clamp is opened immediately. After recovery of function, the clamp is closed again gradually.

After asymptomatic closure of the clamp for 18 to 24 hours, the aneurysm is exposed by craniotomy. Intracranial pressure is reduced via an indwelling lumbar puncture needle. As the lesion is being approached, the blood pressure is lowered to 90-70 mm. of mercury by an intravenous drip of trimethaphen (Arfonad). After exposure and dissection of the lesion, its neck is closed, if possible, by a silver clip or a silk ligature, whichever seems better adapted to the situation. Should the aneurysm rupture, its parent trunk may require clipping. With added experience, this has proved to be necessary less often than in the past. After treating the aneurysm, the patient's systemic blood pressure is restored to normal. The cervical carotid clamp is opened. The brain is re-expanded by introduction of isotonic saline solution through the lumbar puncture needle or into a ventricle. The wound is closed, and the clamp is removed from the carotid artery in the neck. On the 7th to the 10th postoperative day, angiography is repeated via the affected carotid artery only, to be sure the aneurysmal closure has been effective.

SUMMARY

This series of cases demonstrates that even in hospitals admitting patients within a few hours of the onset of subarachnoid hemorrhage, persons having angiographically demonstrable aneurysms can be treated surgically with a higher salvage rate than is expectable with other forms of treatment.

Sixty-nine cases of angiographically demonstrated intracranial aneurysms are reported on. Fifty-one patients were treated surgically, with a mortality rate of 21.5%. In 18 cases the lesions were not treated definitively; the fatality rate was 61%.

In eight cases the aneurysms had not bled; surgery was successful in all of them.

In 43 cases the aneurysms had bled. Surgery in the first week after hemorrhage in 7 cases was followed by a 72% fatality rate; in the second week, in 6 cases, by 33%; in the third week, in 12 cases, by 17%; in the fourth week, in 4 cases, by no fatality, and thereafter, in 14 cases, by 15%. The time of operation after hemorrhage is a crucial factor in survival rates.

Direct occlusion of the aneurysmal neck where possible is considered the method of choice. Carotid ligation is reserved for subclinoid aneurysms only.

The Propagation of Cortical After-Discharge Through Subcortical Structures

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INTRODUCTION

After-discharge arising from electrical stimulation of the cerebral cortex has been extensively studied, with particular emphasis on its cortical propagation and electrical characteristics. That it may implicate subcortical neuronal ganglia has been mentioned by a number of investigators, but careful studies of its subcortical propagation are rare. The present study was designed to investigate the spread of the discharge from different cortical areas to subcortical structures, particularly the basal ganglia.

Our previous experiences with after-discharge have emphasized the necessity of using animals which have had no previous operations or experiments upon the nervous system, and which are not under the influence of drugs that might modify the direction and degree of propagation of the after-discharge. In a previous study of the phenomena, we found that in animals made epileptic by the application of aluminum oxide (alumina) cream to the cerebral cortex, or in which repeated epileptic attacks had been induced by electrical or chemical means, the after-discharge did not stop simultaneously, as usual, in all regions, but continued as a self-propagating "will-o'-the-wisp" response through the cerebrum. Anesthesia also influences the after-discharge. Rioch and Rosenbleuth[16] noted that chloralose anesthesia tended to give prolonged motor after-discharges, a finding which has been confirmed by other investigators. Diallylbarbituric acid (Dial), according to McCulloch,* may induce a self-propagating type of after-discharge. Barbiturates, even in small amounts, tend to depress the spread of the after-discharge. Although curare has been said to cause hypersensitivity of the cerebral cortex,† in our experience curare and/or curare derivatives has produced no abnormal activity after the initial five minutes.

METHOD

This report is based upon the study of eight normal immature monkeys (Macaca mulatta) weighing 6 to 8 lb. All surgical procedures were made after local infiltration of the skin with 1% procaine hydrochloride. The blood pressure was maintained by a slow intravenous drip of dextran and isotonic saline. After a tracheotomy, the animal was artificially ventilated as chemical immobilization was accomplished. Four monkeys were paralyzed with tubocurarine U. S. P. (*d*-tubocurarine) and four animals with succinylcholine chloride, given in sufficient doses to maintain an absence of somatic and respiratory movements.

Cortical electrodes were placed by drilling a small hole through the calvarium and inserting a phonograph needle electrode, which usually just penetrated the dura mater. Bipolar concentric electrodes (0.65 mm. outside diameter) were inserted into the subcortical structures by means of a stereotactic apparatus. These electrodes were left in place throughout the experiment. Recording was

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* McCulloch, W. S., in discussion on paper by Walker and Johnson.[20]

† MacLean, P. D.: Personal communication to the authors.

not started for at least an hour after insertion of the electrodes.

With the electrodes left in place, the animals were killed and the brain perfused with isotonic saline and a 10% solution of formalin. The brain was embedded in celloidin and cut at 30μ; every third section was saved and, routinely, every sixth preserved section stained for myelin and an alternate section for cells by Nissl's technique. Intervening sections were then stained if necessary in order to locate the position of the electrodes.

In each case a sketch was made of the cerebral cortex, indicating the position of the cortical electrodes, and a diagrammatic sketch was made of the serial sections, marking by arrowheads the location of the tips of the needles. Since recording was from the tip of the central electrode to a point on one side of the shaft approximately 1.5 mm. from the end, the tip and base of the triangular arrowheads represent the points of recording.

All recordings were made on two Grass eight-channel electroencephalographs connected so that they could be turned on simultaneously. Most of the records were taken with a time constant of 0.1 second and with a filter reducing the voltage of the high frequencies 50% at 70 cps.

For stimulation a thyratron discharge having a pulse duration of approximately 3 msec. was employed. In some experiments a square-wave stimulus was used, having a pulse duration of 1 or 2 msec. The frequency with both these types of stimulator was usually 30 cps. The voltage varied from 2 to 8. The stimulus was always applied for five seconds. Individual stimuli were carried out seriatim, with a wait between each excitation until the electrical state of the cortex had returned to its prestimulation frequency and amplitude. Thus, no stimuli were given closer together than one minute, and usually two to five minutes or longer elapsed between successive stimulations.

Ordinarily it took approximately three hours to prepare the animal for experimentation, and the experiment continued for six to eight hours following this initial preparation. During this period of time the results of recording appeared to be stable and did not vary greatly. However, when the cortical activity became quite low, the propagation of electrical discharges seemed to be definitely decreased and of a more limited nature.

RESULTS

It is obvious that with intense stimulation the electrical activity of the cortex and subcortical structures is so pronounced and so extensive that it is impossible to determine any pathways of predilection and any systemic involvement which may occur. Accordingly, for this study we have utilized electrical stimuli just sufficient to give rise to an after-discharge lasting from a few seconds to as long as 20-30 seconds. It should be emphasized that usually the cortical after-discharge was associated with discharge in one or more subcortical nuclei.

Characteristics of After-Discharge

The phenomenon of after-discharge is not yet well understood; whether it represents repetitive self-propagating discharges of individual neurones or restimulation of neurones through reverberating circuits is not clear. It is obvious that the phenomenon becomes better developed as it is repetitively induced. In the experimental animal the first few stimuli with shocks well above the threshold of the cortex produce poor or short-lived after-discharges. After these initial limited responses the after-discharges become more easily obtained, last longer, and spread with greater facility to subcortical structures. After some hours there is the tendency for the after-discharge to spread readily through many systems, so that preferential pathways may be poorly defined. However, when the general condition of the animal becomes poor, the after-discharge is shortened, its morphological characteristics are changed, and the threshold is increased.

In Rosenbleuth and Cannon's [17] classical paper on the cortical response to electric stimulation, the after-discharge was described as passing through several stages, the first being composed of fine, rapid oscillations, from 18 to 30 per second. This activity then progressively increased in amplitude, often showing beats having a slow period and waves at a frequency of 6-15 per second. Following this, there was a stage of irregular activity of high-amplitude, fast spikes and slow components, which tended to group themselves into complexes. After the abrupt ending of the response, there was a marked decrease in the spontaneous activity of the cortex. The authors correlated the clonic stage of the attack with the complex or bursts of spikes, but the tonic stage did not correspond to the initial fast, continuous

oscillations or to the period of increasing amplitude of the somewhat slower oscillations that followed. In these experiments chloralose was used for anesthesia, but the same stages have been described by other authors, who did not anesthetize their animals.‡ In the above experiments we have not been able to define the early stages of the after-discharge as clearly as Rosenbleuth and Cannon.[17] The initial fast activity was rarely seen in our preparation. Usually the after-discharge occurred with a series of waves from 6-16 per second, which very shortly broke up into complexes of spikes and slow waves. Our failure to elicit the first stage may be due to the use of a paralyzing agent, or more probably to the fact that our stimuli were just superthreshold. The other stages were consistently present in our records.

The characteristics of the after-discharge varied in the different parts of the cerebral cortex and in the various subcortical nuclei. Our records would confirm the previous descriptions of the types of after-discharge from the hippocampus and amygdala, as given by Kaada,[11] Cadilhac,[4] Liberson and Akert,[12] and Andy and Akert.[2] Perhaps it should be emphasized that often the spiking of the hippocampus and amygdala was at a rate that did not correspond in any respect with the frequencies present in the cortical after-discharge. Within the caudate nucleus the after-discharge occasionally consisted of spiky waves, but in some instances slow waves, having the frequency of the cortical spike-wave complexes, were observed. Usually the caudate activity paralleled that of the frontal granular cortex, which was not necessarily synchronous with the after-discharge in other parts of the cortex. The activity of the caudate nucleus usually stopped with the cessation of the after-discharge in the cerebral cortex, but at times it persisted afterward for some seconds, or even minutes. The induced activity of the putamen usually consisted of high-voltage spikes practically synchronous with those of the ipsilateral central cortex. It followed the changing pattern of discharge of the motor cortex faithfully and stopped simultaneously with it. The thalamic (lateral nuclear mass) after-discharge consisted of spikes and runs of slow waves of lower amplitude but of a frequency similar to those seen in the putamen and central cortex. Usually, but not always, all three stopped simultaneously. In the pons and cerebellum the after-discharge usually consisted of a group of spikes synchronous with the larger spiky complexes of the frontal and central cortex. The rapid cerebellar activity seen in association with systemic strychninization was very rarely observed in the cerebellum or in the pons. After-discharge of the hippocampus and amygdala at times initiated discharges in the hypothalamus and thalamus, where spikes occurred irregularly or in sequence, being rarely synchronous with those of the hippocampus or amygdala.

The temporal relationship of the spiking in the various nuclei was of interest. During the first stages of cortical activity the discharges of subcortical nuclei were rarely synchronous with those of the cortex. However, as the cortical spiky activity decreased in frequency, the discharges of the subcortical nuclei tended to become synchronous with those of the cerebral cortex. This synchrony between the cortex and subcortical structures was particularly pronounced in certain systems, such as central cortex and putamen, frontal cortex and caudate nucleus, and temporal cortex and amygdala-hippocampus. If this synchrony broke, one or both structures continued discharging at independent frequencies. This was particularly apt to occur in the hippocampus or amygdala, which, after a few initial spikes more or less synchronous with activity in some part of the cerebral cortex, developed an after-discharge at a higher frequency than that of the primary discharging focus. As an indepedent discharge developed in the subcortical nucleus, the propagated spiking initiated by the primary discharging nucleus might be abolished. In other instances, as the independent discharge in the subcortical nucleus became less

‡ References 10, 14, and 15.

in amplitude and frequency, the propagated discharges from the primary site of stimulation reappeared.

Although the electrical characteristics of after-discharge resemble closely those seen in epileptic discharges, the two are not identical. The epileptic activity starts with bursts or runs of spikes, gradually increasing in amplitude, and inducing firing in other centers when a certain magnitude of activity is gained; the after-discharge usually begins at a maximum and gradually decreases §; secondarily stimulated ganglia are usually already firing at the onset of the after-discharge. The epileptic activity seems to have a greater propensity to go through long and complex circuits than the after-discharge, which fires one or more nuclear masses seriatum, depending upon the site of stimulation. The epileptic discharge appears to follow anatomical pathways through many nuclei with greater facility than the after-discharge. It is perhaps this breakdown or decrease of synaptic resistance that is most characteristic of the epileptic discharge. One must therefore utilize the findings of after-discharge with caution in the study of convulsive phenomena.

Propagation of After-Discharge from the Frontal Granular Cortex

The frontal granular cortex was stimulated in seven animals. The most constant path of propagation was to the opposite frontal cortex, and this firing occurred in 21 of 24 stimulations. The next most frequent cortical site of induced discharge was the ipsilateral motor cortex (approximately 50%). Much less commonly, the temporal pole was involved. Of the subcortical structures, the ipsilateral caudate nucleus was fired most frequently. At times, this activity consisted solely of low-amplitude spikes or waves synchronous with the cortical spikes, and at other times, of bursts of spikes and waves. Many subcortical nuclei may be involved, but more commonly the amygdala, hippocampus, nucleus medialis dorsalis of the thalamus, putamen, and basal brain stem nuclei (Figs. 1 and 2).

Stimulation of the orbital surface of the frontal lobe induces spiky discharge in the ipsilateral caudate nucleus, hippocampus, and amygdala, and, to a less extent, in the contralateral orbital cortex and ipsilateral prefrontal cortex (Figs. 3 and 4).

Propagation of After-Discharge from the Central Cortex

The paths of epileptic discharge from the pre- and postcentral gyri appear to be essentially the same, and hence the central gyri will be discussed as a unit. Stimulation of this cortex usually induces discharge of the contralateral homologous areas (Fig. 5), although rarely the after-discharge may be confined to the side of stimulation. At times the ipsilateral frontal cortex is implicated, and somewhat more frequently the posterior parietal cortex. The after-discharge evokes consistently a concomitant discharge in the ipsilateral putamen—in fact, in 95% of instances in which after-discharge has been produced, there is concomitant involvement of the ipsilateral putamen. It would seem that the entire putamen fires upon stimulation of any part of the motor cortex. The involvement of the thalamus in its lateral portions is not quite as consistent, occurring in approximately 30% of the stimulations. The subthalamic bodies seem to fire usually with the stimulation of the central cortex. However, the absence of stimulation of the caudate nucleus, of the hypothalamus, and of the amygdala-hippocampus is the rule. The temporal cortex ordinarily does not become involved in the discharge of the central cortex. Stimulation of the motor cortex rarely induces excitation of the amygdala-hippocampus system or of the amygdala alone, as seen in Figure 6. In this case one sees firing of the ipsilateral and contralateral motor cortex, of the ipsilateral and contralateral putamen, and of the ipsilateral amygdala, with, however, no firing of the hippocampus of the same side. The other cortical leads show no abnormal activity, and there is

§ From the electrodes, at the site of stimulation, the initial maximal after-discharge is often not apparent because of blockage of the amplifiers.

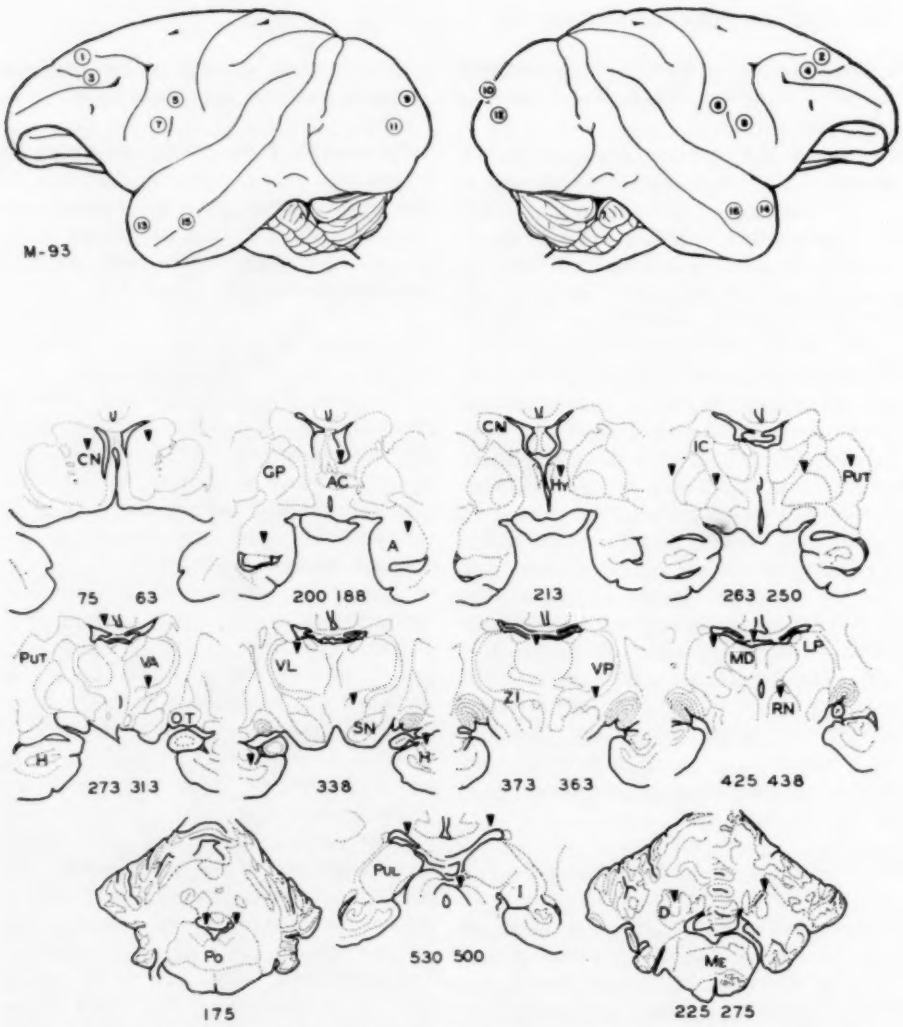

Fig. 1 (M 93).—Diagrams to show the position of the cortical and subcortical electrodes in Monkey 93. In slide *75-63* the caudate electrodes are indicated; in *200-188*, the amygdala and right ventricle-septum electrodes; in *213*, the right hypothalamic electrode; in *263-250*, the putamen and internal capsule electrodes; in *273-313*, the left cingulate gyrus and right nucleus ventralis anterior electrodes; in *338*, the hippocampal, left nucleus ventralis lateralis, and right zona incerta (1) electrodes; in *373-363*, the left medial dorsal nucleus-fornix and right zona incerta (2) electrodes; in *425-438*, the left nucleus lateralis posterior, left corpus callosum, and right nucleus ruber—habenulointerpeduncular tract electrodes; in *530-500*, the left corpus callosum, right occipital white matter, and right posterior commissure electrodes; in *175*, the left lingula and right superior cerebellar peduncle electrodes, and in *225-275*, the left dentate and right cerebellar white matter electrodes. A concentric needle was in contact with the posterior vermis. The laterality is as though the observer were looking at the posterior aspect of the sections, so that the right is to the right of the section.

The abbreviations used in the illustrations are as follows: *A*, amygdala; *AC*, anterior commissure; *CL*, nucleus centralis lateralis; *CN*, caudatus nucleus; *D*, dentate nucleus; *GP*, globus pallidus; *H*, hippocampus; *HG*, hippocampal gyrus; *Hy*, hypothalamus; *HyP*, posterior hypothalamus; *I*, nucleus pulvinaris inferior; *IC*, internal capsule; *LP*, nucleus lateralis posterior; *MD*, nucleus medialis dorsalis; *Me*, medulla; *OT*, optic tract; *Po*, pons; *Pul*, pulvinar; *Put*, putamen; *RN*, red nucleus; *SB*, subthalamic body; *SN*, substantia nigra; *VA*, nucleus ventralis anterior; *VL*, nucleus ventralis lateralis; *VP*, nucleus ventralis posterior; *ZI*, zona incerta. *R* or *L* before an abbreviation indicates right or left.

no abnormal activity of the caudate nucleus on either side.

Propagation of After-Discharge from the Temporal Lobe

Stimulation of the temporal convolutions, particularly the anterior portion of the temporal lobe, has consistently given rise to after-discharge within the temporal cortex, frequently in the frontal granular cortex and face area of the motor cortex (50% of instances) and consistently within the amygdala and hippocampus on the same side (85%). With further propagation of the fit, the structures related to the hippocampus and amygdala, namely, the septum, cingulum, and hypothalamus, are involved. The orbital cortex may be activated, in which case the caudate nucleus often participates in the activity (Fig. 7). In the illustration, it is interesting to note that there is no activity in the opposite temporal cortex (Electrodes *21-23*). Consistently, excitation of the temporal lobe tends to activate, first, the ipsilateral hippocampus-amygdala, and then the prefrontal cortex, with eventual activation of the caudate nucleus.

Propagation of After-Discharge from the Occipital Cortex

The pathways of propagation from the occipital cortex have been studied in several animals, but it has been difficult to elicit a long-sustained after-discharge in this portion of the brain. Usually the response is confined to the cortex without spread to other structures, although occasionally the parietal lobe is involved. Generally the response from stimulation of the occipital cortex has been short-lived and much more difficult to obtain than from other portions of the brain. However, we have not examined the activity of

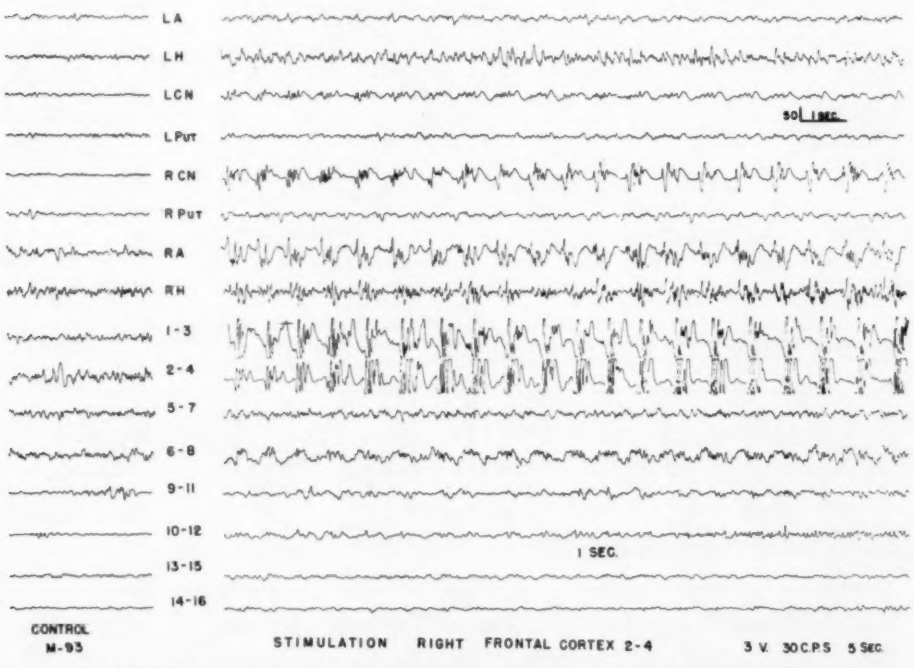

Fig. 2 (M 93).—Electrograms after stimulation of right frontal granular cortex with 3 volts, 30 cps for five seconds to show the cortical after-discharge at the site of stimulation (*2-4*) and the concomitant discharge in the opposite frontal cortex (*1-3*), the ipsilateral caudate nucleus (*RC N*), the amygdala (*RA*), and the hippocampus (*RH*). Fifth stimulation; two hours after insertion of electrodes.

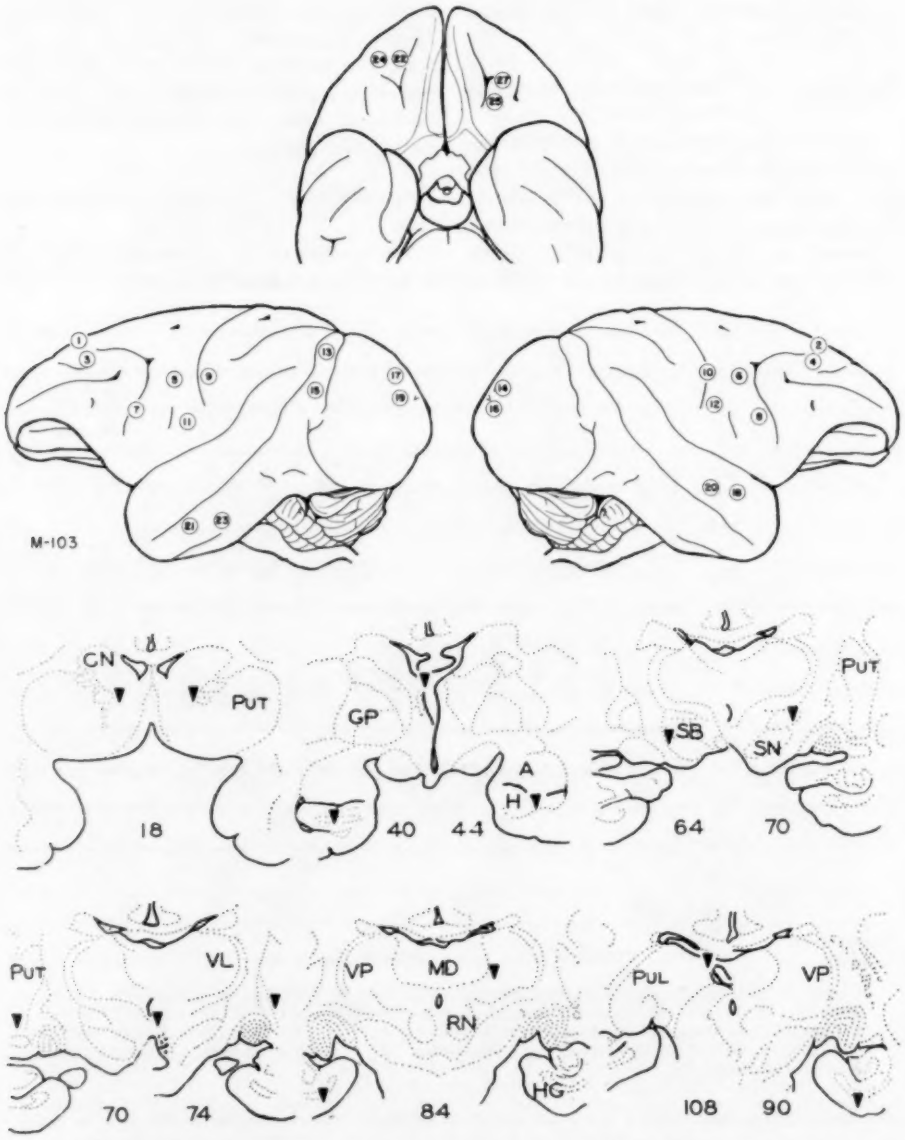

Fig. 3 (M 103).—Diagrams to show the position of the cortical and subcortical electrodes in Monkey 103.

the lateral geniculate body during after-discharge of the occipital lobe.

Spread of After-Discharge

The conduction of the after-discharge is along fiber tracts to the cortex or the subcortical nuclei, but we think the response of these structures depends not only upon facilitation and summation || but possibly also upon the modification of their excitability related to the physical non-neuronal effect of

|| References 3 and 14.

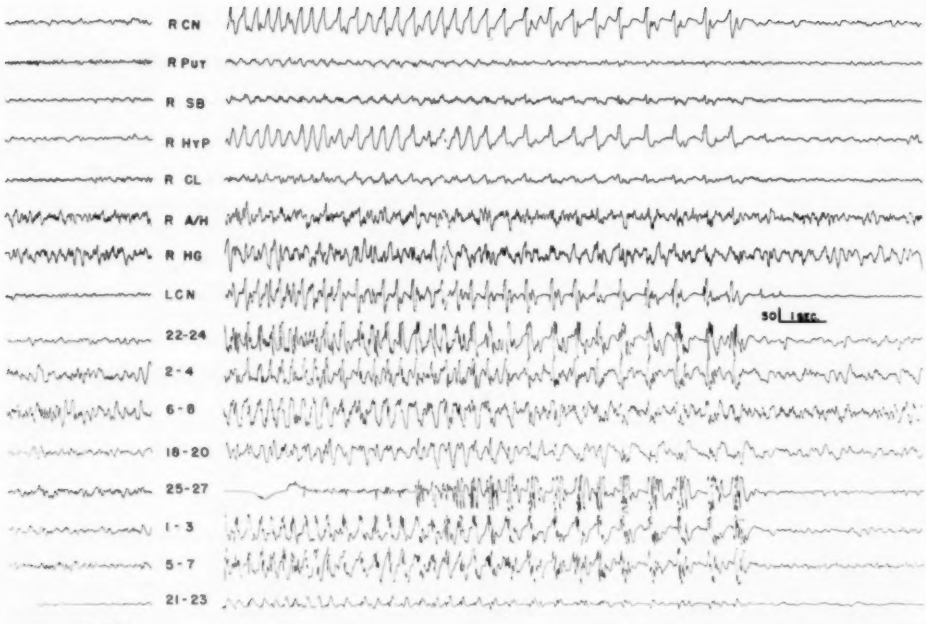

Fig. 4 (M 103).—Electrograms after stimulation of the orbital frontal cortex with 7.5 volts, 30 cps. for five seconds to show the after-discharge at the site of stimulation (*25-27*), the discharge in the contralateral frontal cortex (*22-24*) and convexity of the granular frontal cortex (*1-3* and *2-4*) and the smaller degrees of discharge in the other cortical areas, and the discharges in the caudate nuclei (*L CN* and *R CN*) and right hypothalamus (*R HyP*).

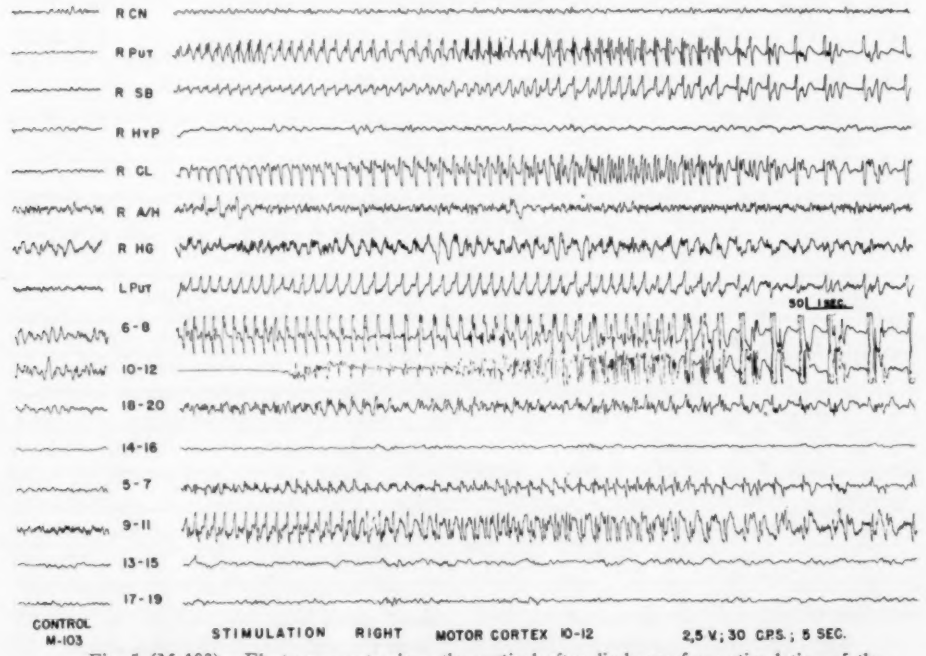

Fig. 5 (M 103).—Electrograms to show the cortical after-discharge from stimulation of the right face motor area (*10-12* and *6-8*) and the discharge from the opposite motor cortex (*9-11*); the discharge of the right putamen (*R Put*), the right nucleus centralis lateralis (*R CL*), and the left putamen (*L Put*), and the gradual build-up in the right subthalamic body (*R SB*).

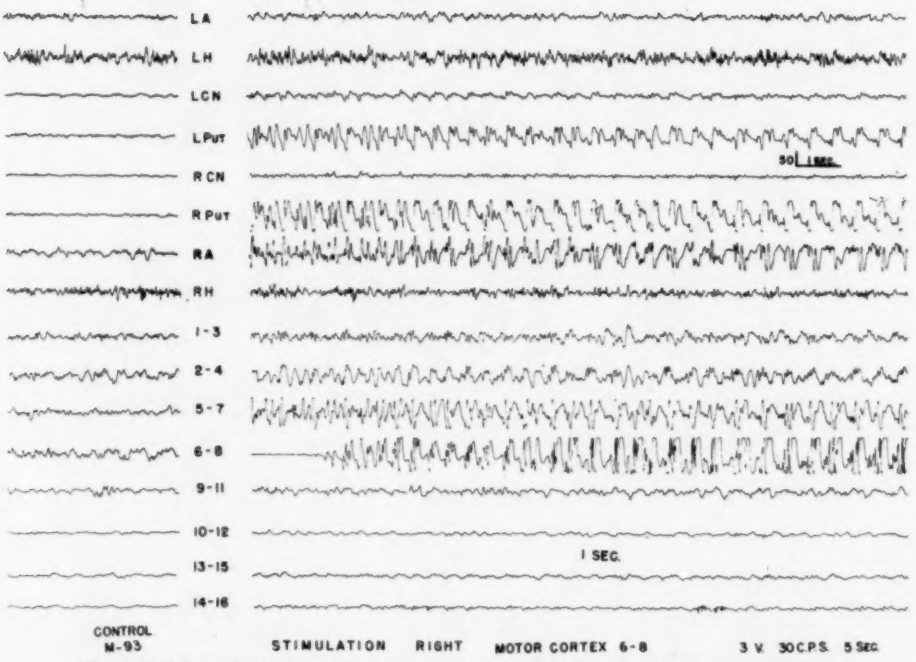

Fig. 6 (M 93).—Electrograms of Monkey 93 to show the cortical after-discharge from stimulation of the right motor cortex (*6-8*) and the concomitant discharge of the two putamens and the ipsilateral amygdala (*RA*).

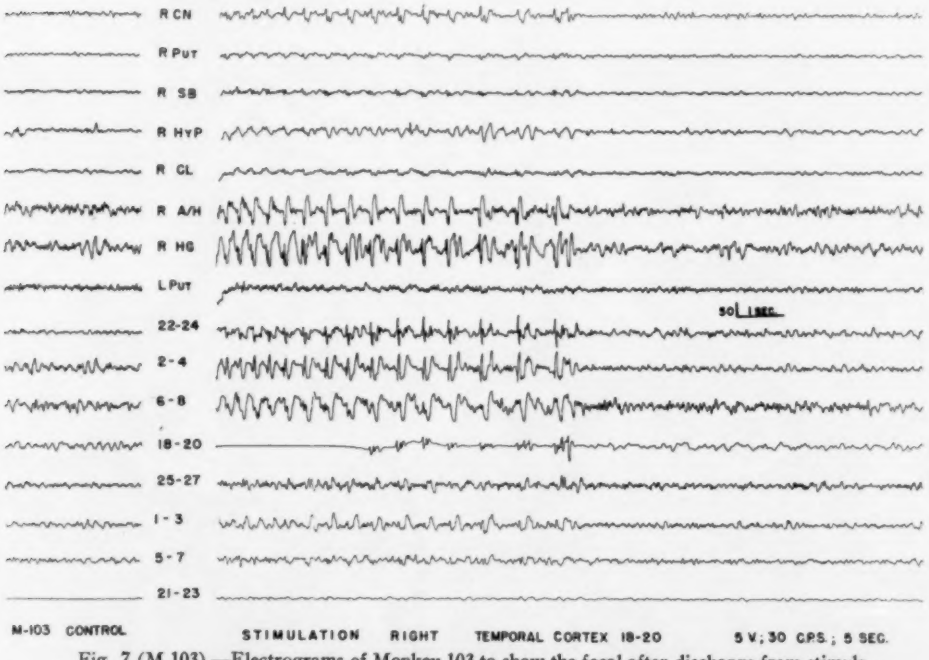

Fig. 7 (M 103).—Electrograms of Monkey 103 to show the focal after-discharge from stimulation of the superior temporal convolution: ipsilateral frontal granular, ipsilateral face premotor cortex, and ipsilateral amygdala and hippocampus. Minimal activity is seen in the caudate nucleus.

the stimulus. In Figure 5 the gradual build-up of activity in the right putamen and subthalamic body is probably due to all of these phenomena.

In the cerebrum, after-discharge seems to involve large neuronal masses, and rarely is confined to a few nerve cells. The mechanism by which practically the entire motor cortex of one hemisphere or the prefrontal cortex on both convexity and orbital surfaces becomes simultaneously a discharging mass is not clear. It is apparent that the cortex may be bombarded by many volleys from an after-discharging homologous cortical area with any degree of participation in the phenomenon. This is true also of subcortical ganglia, which are stimulated to after-discharge only by volleys of supraliminal intensity firing the entire nucleus. Not infrequently the motor cortex and ipsilateral putamen have discharges without spread to the ventrolateral nucleus of the thalamus. Similarly, the hippocampus may have localized discharge without spread to temporal cortex or septum.

The old concept of the cortical discharges firing into a subcortical pool which produced a generalized seizure is not confirmed by this study. Rather, the main cortical areas seem to have preferential pathways of propagation to different subcortical structures, which become activated independently. Only when the several cortical-subcortical systems are implicated does a generalized seizure result.

COMMENT

Preferential Pathways of Propagation.—It seems from these experiments that certain preferential subcortical pathways of after-discharge occur upon cortical stimulation. From the prefrontal and orbital cortex the caudate nucleus of the same and opposite sides is involved, and the hippocampus-amygdala complex. Although the first pathway has not been noted previously in the primate, Jung [10] states that the caudate nucleus is always involved if the thalamus or the isocortex discharge. This may be true for the cat, and our experiences have confirmed that the caudate nucleus is consistently involved in after-discharge induced from the anterior part of the cat's cortex. Stoll and associates [19] describe a caudate response to after-discharge of the cat's temporal cortex. The relationship of the orbital surface of the frontal lobe to the temporal cortex and amygdala-hippocampus complex has been emphasized by a number of previous investigators. MacLean,[13] particularly, has called attention to the interrelationships of these areas, since he believes that the fronto-temporal region is a part of the "visceral brain." The bilaterality and multiplicity of subcortical involvement with unilateral after-discharge in the frontal granular cortex should be emphasized, since it may be related with the early loss of consciousness in patients having epileptic seizures as the result of lesions of this area. Frequently discharges are recorded from almost all subcortical nuclei being sampled — caudate nucleus, medial nucleus of the thalamus, hypothalamus, hippocampus and amygdala, limbic cortex, and cerebellum.

That the after-discharge from the central gyri involves preferentially the contralateral homologous cortical areas has been recognized for many years and emphasized by Erickson.[6] But that there is a preferential firing of the putamen with discharge of the motor cortex has not been recognized, although the Japanese workers—Hayashi,[8] Jinnai and associates,[9] and others—have suggested, on the basis of extirpation studies on dogs, that the lenticular nucleus is essential to the propagation of a fit and advised lenticulotomy for the treatment of epilepsy. The participation of the thalamus in the after-discharge of the central areas was noted by Walker and Johnson,[20] who thought that a thalamic nucleus fired in association with its cortical projection area. However, on the basis of these studies, the thalamus would seem to be involved together with the putamen, and hence its discharges may be secondary to excitation of that nucleus, and probably not necessarily on the basis of corticothalamic connections. Whether the thalamic activity then activates the cortex, again, cannot be stated from this study. In the cat,

Jung [10] described 6-12 per second activity in both medial and lateral thalamic nuclei associated with cortical after-discharge.

The preferential pathways of discharge following temporal lobe excitation would seem to involve the amygdala, hippocampus, and the structures related to the efferent systems of these nuclei, namely the fornix, anterior hypothalamic region, cingular gyrus, medial thalamic nucleus, and septum. Many investigators have found such pathways of propagation in rabbit,[7] cat, and monkey.¶ Cadilhac [4] traced the discharge to striatum, superior colliculi, and thalamus. Segundo and associates [18] believe that the preferential pathways from the superior temporal gyrus are to the homolateral putamen, globus pallidus, amygdala, hippocampus proper, and hippocampal gyrus. Little or no propagation of activity to these structures was obtained from the second temporal gyrus. We have not been able to define the effects upon cortical stimulation so precisely, as most of our observations have been from electrodes on the superior temporal gyrus and temporal pole. However, we have not observed the putamen, caudate, or globus pallidus activity in more than 10% of stimulations of the temporal cortex.

It is obvious from a superficial survey of the pathways of propagation following stimulation of the various cortical areas that relatively few of the available pathways are utilized by the after-discharge. The physiological determinants of these preferential pathways are not apparent at this time. It is, however, evident that under certain circumstances, particularly intense stimulation, the pathways may be much more widespread, or even generalized.

SUMMARY

The characteristics and interrelationships of cortical and subcortical after-discharge are discussed on the basis of observations on the immobilized macaque monkey having multiple depth and surface electrodes. The electrical after-discharge from the frontal, central, temporal, and occipital cortices spread to different subcortical nuclei. Three main "preferential pathways" of propagation could be recognized: from the frontal granular cortex to the nucleus caudatus, from the central cortex to the putamen, and from the temporal cortex to the amygdala-hippocampus complex. Other subcortical nuclei less consistently participated in the propagated discharge.

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Pharmacotherapeutic Evaluation and the Psychiatric Setting

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Once again we are immersed in a period of intense interest in pharmacotherapy in psychiatry. The recent advent of chlorpromazine, reserpine, pipradrol (Meratran) and its derivatives, meprobamate (Miltown), etc., has catalyzed interest in the field, and our specialty journals are filled with enthusiastic reports. Physicians in diverse medical specialties frequently prescribe these drugs to patients with almost any variety of affective component in their symptom pattern. Such an intensely hopeful response once again reflects the unfulfilled therapeutic needs of the psychiatric profession, which potentiate the hope of quick closure for many problems. It is natural to empathize with those persons responsible for therapeutic programs in our state hospitals when they become enthusiastic over a new type of therapy. They have the greatest needs and the largest immediate responsibility of the profession. At present, as a group, they are very enthusiastic about the new drugs, and this is of profound social importance. It prompted Nolan Lewis at a recent meeting to use the old adage, "You should treat as many patients as possible with the drugs while the effects still last." At any rate, the field is afire with new interest, and this may be as important as the new drugs themselves.

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At the Institute for Psychosomatic and Psychiatric Research and Training, however, no such enthusiasm has been generated. Six months ago we sent out a questionnaire to our staff in an effort to assess its experience with the newer drugs. Chlorpromazine had been prescribed for a total of 51 patients, two-thirds of whom were outpatients. The staff psychiatrists, as a group, reported quite poor results, and in general they were unimpressed with the effect of the drugs.

During the past six months we have evaluated the use of both chlorpromazine and reserpine on inpatients. Our present data comprise essentially anecdotal and descriptive material on 60 patients, 42 of whom received chlorpromazine and 18 reserpine. The nosological grouping of the patients includes a fairly representative sample of our patient population; thus, 38% were depressive patients, of whom two-thirds were of the agitated variety, and 29% were schizophrenic; in 20% the diagnosis indicated high degrees of anxiety, 8% had organic brain diseases, and 5% were manic. In terms of agitation, 5% of the patients showed none, 36% mild, 42% moderate, and 17% severe. The highest dosage of chlorpromazine was 400 mg. a day, while the highest dosage of reserpine was 16 mg. a day. Only 5 of 42 patients on chlorpromazine received the treatment over 30 days. Of the 18 patients on reserpine, 7 received the drug over 30 days.

Since the differences between the effects of chlorpromazine and reserpine were indistinguishable, we shall present them as a composite group. Forty per cent of the patients showed no effects or side-effects alone.

Another 40% showed a minimal to moderate sedative effect. Twenty per cent had moderate sedative effects, which were deemed by their therapist to have played an important role in the patient's recovery. Of these 12 patients, 10 had intensive psychotherapy. Of the entire group, about 35% had intensive psychotherapy concomitantly. The factor of concomitant therapy is further illustrated by the fact that 40% of the patients receiving the drugs were also given electroshock at one time or another during the hospitalization. Thirty-five per cent of the patients depended regularly on additional daytime sedation, and it was the rare case that did not require additional night-time sedation. Eight patients with Grade 3 (severe) agitation were included in the series. Six of these showed moderate quieting effects with a definite reduction of their agitation, but of the eight, seven required electroshock during the hospitalization. Of the six agitated patients who responded to the medication with moderate sedation, three were subsequently sent to state hospitals.

Many of our staff have been struck by the similarity of the present period of drug enthusiasm with that at the introduction of insulin, pentylenetetrazol (Metrazol), corticotropin (ACTH), histamine, mephenesin (Tolserol), the barbiturates (especially amobarbital), carbon dioxide, ergotamine, and the amphetamines. The first reports tended to be enthusiastic. They emanated, primarily, from institutions with the greatest need for immediate results. After several years the limitations for use became more apparent, and some of the above-named drugs have been relegated to limbo in psychiatry.

We have been struck by the extent of the contrasting attitudes and findings of our own staff and those of others reporting on the new drugs. We felt that an exploration of the effects of the variations of milieu upon the new drug treatment might explain the discrepancies. Hence the main purpose of this paper is to contrast our hospital with other psychiatric settings with special reference to the use of the newer drugs.

Our assumptions may be stated in this way: At the present time the vast majority of psychiatric illnesses have no specific treatment in the traditional medical sense, i. e., such as penicillin for Pneumococcus infections. Integration and improvement are accomplished by several transacting processes, and require social reinforcement through time for maintenance. We believe that this concept is valid, irrespective of the types of psychiatric therapy employed. Even for lobotomy success of therapy is conditional on the attitude of persons in the same environment to which the patient is discharged. Hence it seems fallacious to shift frames of reference when somatotherapies are used. By this we mean that the concentration on the neuropharmacological level and the minimizing of other processes when one prescribes drugs may bring about distortions in the evaluative judgment. Paradoxical effects occur, depending on the prior state of the patient receiving the drug. Additional shifting effects occur when the milieu is varied. We feel that it is a rare type of somatotherapy that transcends the milieu and produces consistently independent clinical improvement. Drug effects seem much less specific, even though on very high dosage the toxic signs are fairly uniform irrespective of environment. To give one illustration of this point, Wolf and Wolff [1] have shown that their gastrostomy patient, Tom, had varied gastric responses in different situations. He showed paradoxical responses to drugs, depending upon the moment-to-moment relationship with the examiner. We are aware that many of these statements seem self-evident, but the implications of these assumptions are not accepted in the day-to-day use of somatotherapy in psychiatry.

Let us now contrast the setting in our hospital, which will be abbreviated in the paper as P&PI, derived from Psychosomatic & Psychiatric Institute, with that of certain typical state hospitals. P&PI is part of a general hospital but is housed in a separate building. There are 80 beds, of which 80% are private. About 750 patients are admitted

each year, and they are treated by a large attending staff of psychiatrists. The latter have been trained primarily with a psychoanalytical orientation. There is an additional courtesy staff of physicians whose training background varies. There are 15 psychiatric residents and a relatively large staff of nurses, O. T. workers, aides, and other ancillary therapeutic personnel.

PATIENT POPULATION

Patients admitted to psychiatric sections of general hospitals are qualitatively different from those seen in the state hospitals. Irrespective of the nosological groupings, patients who enter general hospitals tend to be in a more acutely disruptive phase of illness. The vast majority of state hospital patients have reached a steady state of illness even if their behavior remains bizarre, agitated, or querulous. Our knowledge of the long-term aspects of psychiatric illnesses is limited, and we know very little about what processes maintain the patients in a psychotic steady state for a long time. Nevertheless, there may be a host of paradoxical responses to drugs, dependent upon the different phases of the same nosological entity.

Other elements in patient population besides the phase of illness are crucial in assessing the effect of any new therapeutic variable. As a group, the patients at P&PI are more conversant with psychotherapy as a process, although they are not as homogeneous in this respect as patients in some other centers. Stanton and Schwartz [2] point out that at Chestnut Lodge treatment is equated by the patients with psychotherapy. In the patient's value system somatotherapies rank quite low. At P&PI there have been several examples of patients who became angry with their doctors when they were placed on drug treatment. They thought that this was deprecatory to them. For example, the 55-year-old wife of a local physician was recently admitted in an agitatedly depressed state. She had had intensive psychotherapy 10 years previous to the admission. When she was placed on chlorpromazine, she was bitterly resentful. This implied to her that she had a poor prognosis and that she was being treated in a "second-class way." On the other hand, P&PI and general hospital patients tend to differ from patients at places that are considered more as homes, foundations, schools, or lodges. A large number of our patients see us clearly as part of a hospital, and some have a strong expectancy of the more traditional type of medical treatment. This, of course, facilitates the use of drugs.

Our patients stem from good economic circumstances, and the great majority pay for their psychiatric care. Redlich [3] has clearly illustrated how the type of therapy employed may be related to the class background or economic circumstances of the patient. Economic pressure may force the psychiatrist to choose a quicker form of therapy if the hospital stay must be curtailed. In this context, it should be noted that chlorpromazine and reserpine often require a lengthy clinical trial. At times the necessary length of treatment cannot be maintained at the private hospital.

There are several other aspects about our patients that facilitate the use of psychotherapeutic methods. The patients in general hospitals and at P&PI tend much more frequently to be hospitalized for the first time. They differ from state hospital patients in possessing superior reality testing, ego flexibility, internal resources, and previous successful adaptive modes. Consequently, they possess greater social communicability, which allows them to participate more in psychodynamically oriented therapy.

As our patients are treated closer to their homes than are most state hospital patients, the relatives may be better integrated in the total treatment plan. This facilitates the use of psychotherapeutic methods if the chances for alteration of the home surroundings of the patient are good.

ENVIRONMENTAL FACTORS

Each psychiatric treatment center has a therapeutic aura which is a concatenation of

many factors. The milieu at P&PI is more complex than usual, in that we stand at the crossroads of several divergent approaches. At the roots of our organization we are medically grounded, and there is much in our structural organization which reflects general hospital attitudes. On the other hand, we possess a larger measure of autonomy than is usual for a psychiatric section of a general hospital. This permits the infusion of psychodynamic principles, and also permits the utilization of types of inpatient policy novel for general hospitals. In effect, the multiplicity of approaches has allowed a rather wide base of therapeutic alternatives.

For many people on our staff, however, there is a distasteful aspect to the utilization of somatotherapy. As an example, one of the nurses said that the only somatotherapy that she felt positive toward was insulin therapy. She elaborated by saying that it was not the insulin per se that was approved, but the fact that the patient had eight hours of close contact with another person during the treatment. This staff attitude is communicated through the various levels of personnel to the patients and affects the drug responses. The attitude of a particular staff defines its position in reference to many conflictual areas in the field of psychiatry. It is clear that both subtle latent conflict and more overt problems emerge when new treatments are discussed. People identify strongly with modes of therapy. Let us now look at the attitudes at P&PI and compare them point by point with some state hospital values.

1. Activity Rate of Staff-Patient Interaction

At P&PI the average patient has an active daily program. He sees his therapist and unit personnel quite often. He goes to occupational therapy frequently and participates in a host of activities and interpersonal relationships. The addition of a drug into this complex field makes it difficult to isolate the specific effect of the drug. In the state hospital the introduction of a new drug is often made into a vacuum of relative inactivity. The patient has achieved a certain steady state, and there is lack of personnel to provide a variety of activities. Hence drug changes are more easily ascribed to the drug per se, as it is deemed the only new variable. We say "deemed," as it is our contention that the attitude of the staff toward the drug is an equally important variable. The addition of a new drug at P&PI is often looked upon unenthusiastically as a questionable and unimportant addition to an already full schedule, and to many on our units it seems like a chore. This contrasts with many state hospitals, where the drugs have markedly raised the hopes of therapeutic success.

2. Staff Tolerance of Agitated Behavior and Immediate Goals of Treatment

In the state hospital the lack of adequate personnel and the presence of large numbers of extremely disturbed patients make it imperative that immediate limits be placed on various types of hyperactivity. The implicit and explicit goals of treatment are to keep the unit as near to tranquility as possible. Drugs which tend to diminish psychomotor activity are utilized by the staff as a means to maintain order. At P&PI there is a much greater individualization, with the realization that for many patients "tranquility" may be markedly deleterious. In this context, Spinka,* at another hospital, reports better results in female patients on chlorpromazine. He suggests that male patients may equate tranquility with passivity and a threat to masculinity. Agitatedly depressed patients may respond with increased painful affect to a reduction of the agitated defense. In addition, several reports † have indicated that up to 15% of hypertensive patients have responded to reserpine therapy with depressive reactions. On the whole our patients are encouraged to keep an optimum rate of

* Spinka, I.: Personal communication to the authors.

† References 4 to 6.

activity, and such signs as lethargy and withdrawal are not regarded in the same light as they are in the state hospitals.

It is clear that evaluation of a patient's response to a drug would be affected by the goals of the unit as a whole. These goals shift a great deal. To give an illustration: Often when a single manic patient enters a unit there is a tendency for a period of disequilibrium to occur. During this time the immediate goals of the unit may change quite a bit. Peace and quiet may be more at a premium. We are stressing the shifting goals of our units, in contrast to many state hospital units, where the goals tend to be more constant. Of course, the attitudes of the personnel to specific patients affect individual goals for all the patients. Thus, with certain patients they would be very alarmed at lethargy. In other patients they would very much welcome this sign. Occasionally, the personnel respond to patients with either overt or covert belief that increased dependency gratification would be quite helpful. The giving of a drug, with the attendant procedures accompanying its administration, provides a vehicle to afford such gratification where other channels are blocked. The personnel may then welcome the fact that patients on chlorpromazine and reserpine tend to become lethargic, often requiring bed care. Several of our best results of drug administration occurred in this context.

3. Tolerance for Delayed Effect and Toxicity

Both chlorpromazine and reserpine have a large number of toxic signs. The expectation for a drug plays an important role in the toleration of toxic signs. It is clear that our staff is quite concerned over those toxic signs that we have seen already. Before one will utilize a drug with this kind of potentiality, one must have a positive impression that beneficial effects will be forthcoming. In addition, the less dangerous, but still annoying minor toxic signs are engrafted upon a low frustration tolerance which our personnel possess in this area. Their feelings are readily communicated to the patients. Of course, the way in which these procedures are carried out connotes many things to patients. This has varied from anxiety lest something be seriously wrong with them to the conception of blood-pressure recordings as a highly erotic experience. For example, one female patient had frequent dreams revolving about the administration of reserpine by a male nurse. The dreams were filled with sexual symbolism relating to the frequent blood-pressure recordings. In contradistinction, the state hospital personnel tend to see the minor toxic signs as indicators that they are approaching or have exceeded effective dosages. At a meeting of the Illinois Psychiatric Society, one speaker, Steinfeld,‡ indicated that he greets the development of Parkinson's syndrome with enthusiasm in that he feels that this indicates that the drug has finally achieved effective levels.

Both chlorpromazine and reserpine are often quite slow in producing effective responses. Reserpine especially may take weeks to act. As a matter of fact, in most patients reserpine is said by Barsa and Kline § to produce a state of turbulence, accompanied often by a florid exacerbation of symptoms. Needless to say, it takes a great deal of faith to ride through such stormy periods, unless one looks at the response as an indicator of positive things to come. In our hospital it is a rarity to find a patient who has gone through the gamut of all the available therapies and failed—in marked contradistinction to the state hospital, where such cases are quite common. Hence, at P&PI the tendency is to have hopeful expectation that one of a number of possible alternatives can work, especially psychotherapy.

4. Exploration with Higher Dosage Level

It is clear that at P&PI we have been very conservative with the dosages employed in the newer drugs. This reflects the quantity

‡ Steinfeld, L.: Personal communication.

§ Kline, N. S.: Clinical Applications of Reserpine, presented before the American Psychiatric Association, Section of Medical Sciences, American Association for Advancement of Science, Berkeley, Calif., Dec. 30, 1954.

and quality of the alternative choices of therapy. It also reflects our unwillingness to risk toxic signs from a drug about which we are doubtful. We started with a dosage of 0.25 mg. of reserpine t. i. d. and 25 mg. of chlorpromazine t. i. d. More recently we have gone up to daily doses of 16 mg. of reserpine and 450 mg. of chlorpromazine. We know that other institutions have gone up to doses ten times as high as our maximum doses, i. e., 4 gm. of chlorpromazine and 130 mg. of reserpine a day. In the higher ranges of reserpine doses the toxic signs increased sharply. Some people would explain our lack of dramatic findings on "inadequate dosage." Although we believe that this is only a small part of the picture, we would agree that we have lagged behind some other hospitals in stepping up the dose. We feel that this is a reflection of our attitude toward our patients and the drugs. We do not wish to risk untoward signs when we are surer of the alternative ways to treat outpatients.

5. Intrastaff Relationship and Effect on Therapy

Caudill and associates [7] and Stanton and Schwartz [2] have well illustrated how the patient's course in a mental hospital may be affected by problems in intrastaff relationships. While their frame of reference is largely the effect on the psychotherapeutic processes, we feel that this is also true of the somatotherapies. At P&PI the large staff and multiple lines of communication increase this problem in many ways; this situation is in marked contradistinction to that in the state hospitals, where there are fewer people treating the patients. At P&PI the unit personnel tend to be disappointed if somatotherapies are carried on without an active psychotherapeutic approach. If the psychotherapeutic plan is explicit in defining the roles of the unit personnel, the patient is liable to benefit from more positive feeling about the therapy. This is also dependent on the working relationships of the various people involved in treating the patient. If there is friction, the patients will feel it in one way or another. These working relationships are important in the responses of patients to pharmacotherapy. One of the nurses thought that reserpine was more effective than chlorpromazine. Her opinion stemmed from the fact that two of the patients placed on reserpine on her unit were treated by doctors who worked intensively and effectively with the unit personnel. While the more "objective" evidence of the positive effect of the drug was lacking, both patients received a good deal of extra care. Another physician with extensive drug experience, at a different hospital, has prescribed chlorpromazine for three patients at P&PI. His results were uniformly poor. He tended to explain this difference on the fact that the three patients at P&PI were all depressed. This doctor used much higher doses of chlorpromazine than did the rest of our staff, in view of his previous experience. The nurses reported being alarmed by this dosage. In addition, the doctor involved was not well known by them. We feel that the intrastaff relationships may have been as equally important in the results as the type of patient treated here.

COMMENT

In this paper the emphasis has been placed on certain transactional factors between the individual patient and his environment which raise problems in drug evaluation. This emphasis has largely by-passed the more specific psychophysiological area of drug effects and, in so doing, may have distorted the perspective by relative omission. It is clear that both chlorpromazine and reserpine are not inert drugs. Both drugs seem to have the property of producing a measure of tranquility without some of the more untoward signs of the barbiturates. If this finding is maintained, both the drugs will have found a definite place in psychiatric utilization.

Claims for the drugs, however, have gone far beyond the sedative stage. There have been statements which indicated that the

drugs have certain intrinsic curability. We feel that these claims are premature in several ways. In the broadest sense, the evaluation of the therapeutic effect in any new treatment in psychiatry is subsumed under the question of the methodology of the evaluation. Although, at times, we feel that our techniques for evaluation of results are good, our empirical evidence for this is suprisingly poor. For this reason, of course, the evaluation of any new therapy can be no better than the older available evaluations in the field. The physiological processes involved in the drug therapies are quite obscure. Certainly, we are a long way from an understanding of the neurophysiological correlates of behavior. It is our opinion that the psychodynamic understanding of when to use a drug in the course of therapy is also quite limited. It is the major contention of this paper, however, that special social factors would have to be taken into consideration, even if we had much greater knowledge of both the neurophysiological correlates of the psychiatric disorders and the psychodynamic principles important in the utilization of the drugs. There is a great deal of recent evidence to indicate that other branches of medicine have recognized the importance of some of these concepts. Quite recently, Lasagna and associates || have shown that morphine, heroin (diacetylmorphine), the amphetamines, etc., have varying effects, depending upon the population studied. He gave normal volunteers, chronically ill patients, and postaddicts randomized samples of these drugs and placebo. In normal volunteers the morphine and heroin were experienced as quite unpleasant drugs. In contradistinction, the postaddicts found the morphine quite pleasant. Lasagna illustrated that the addicts are unusual in responding with euphoria to a wide variety of agents, such as analgesics, amphetamines, antihistaminic agents, and even Coca-Cola. We believe that he has clearly illustrated how the prior personality is an important variable in the response to drugs.

|| References 8 and 9.

Gold,[10] in a recent Cornell conference on drug therapy, illustrated that the effect of a drug varied greatly with a patient's mood. He showed how unconscious bias of the physician can affect the results of even so-called objective measurements, such as iron in anemia, and anticoagulants in thrombotic diseases. Lasagna and Gold have emphasized the interaction of the previous personality with the drug being given.

In this paper, we are highlighting another dimension, i. e., the social field in which the patient interacts with the drug. The social factors are not merely added variables but also integral parts of the transactional field of drug response. We agree with both Gold and Lasagna when they call for more rigorous methods in an attempt to eliminate the bias of the observer in the evaluation. We would like to point out, however, that the use of double-blind studies has certain limitations. Thus, when one compares active drugs like chlorpromazine or reserpine with a relatively inert preparation such as saline, problems may develop which stem from the instructions to the personnel and the patients as to what to expect from the drugs. If on a particular psychiatric unit some patients are placed on placebo and other patients on the active drug, the personnel is instructed as to what autonomic signs may occur. The patients, too, are often instructed in a similar fashion. In view of the fact that both chlorpromazine and reserpine affect many systems, these signs become the cue, both to the patient and to the personnel, that these patients are receiving the active drug and not placebo. It is here that interaction may take place among the tester, the attending personnel, and the patient. Often the patient may interpret a change in his internal milieu in the context of being a change in the expected direction. It is thus possible for a subtle type of communication to take place among the various participants, and this may potentiate the drug effect. Hence a relatively nonspecific effect can be geometrically increased. Thus, the hopeful expectancy or lack of expectancy plays a role even in the double-blind studies. It is

necessary to compare drugs such as reserpine and chlorpromazine with very active placebos that simulate some of the reserpine and chlorpromazine action.

The most rigorous experimental designs hitherto used do not entirely control special factors in the evaluation of drugs in psychiatry. A special problem is the particular criteria that one uses for change; i. e., we have indicated that diminution in agitation is not necessarily an adequate prognostic indicator. Length of hospitalization is not adequate, either. Thus, in many of our patients, long-term hospitalization signifies the most intensive treatment, and the goals for therapy may be closer to a basic reconstruction of character patterns. Simple statements of improvement or lack of improvement on discharge and follow-up sometimes may be useful, but have definite limits.

The problem merges into the broader question of how to judge the effect of hospitalization upon the patient's course of illness. We believe that the evaluation of somatotherapy will lag behind the broader problem. We do not mean to imply by this a nihilistic attitude toward the pragmatic utilization of somatotherapy. Nor do we mean to imply that we must have a measure for change that approximates the blood sugar for insulin effect or an EKG for digitalis effect; however, we are emphasizing the need for better criteria than those currently available.

While the major theme in this paper has emphasized caution in terms of the evaluation of the newer drugs, another theme has run through it. It is clear that we feel that a negative attitude toward somatotherapy plays a role in hindering the proper utilization of such treatment. Thus, we have presented relatively negative results from the use of both chlorpromazine and reserpine at our hospital. We have not controlled for our negative attitude, however, and we are just as liable to criticism for saying that our results prove the inefficacy of the drugs as are those people who were overenthusiastic. The phenomenon of negative attitudes toward somatotherapy needs amplification, and we have attempted to illustrate it. We have also illustrated that this attitude is communicated to all levels of personnel at psychiatric hospitals and plays a role in the entire therapeutic aura. We have shown that each inpatient center has its distinct milieu which in a complex way facilitates or inhibits drug usage. Extreme facilitation occurs at places with the greatest immediate needs and the most intense expectations from the drug. The greatest inhibition occurs when there exists strongly negativistic attitudes toward its use, for a variety of reasons.

We believe that the present role of pharmacotherapy in psychiatry is undefined, but perhaps some of the intense response to chlorpromazine and reserpine can be channelized into a fuller understanding of the area.

SUMMARY

Data are presented illustrating the effects of chlorpromazine and reserpine prescription to patients at the Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital. The results have been less positive than most studies reported elsewhere. An attempt is made to analyze factors in the specific psychiatric setting and patient population that might account for these findings. One factor appeared to be the relatively negative attitude of our hospital personnel toward the prescription of drugs as compared with alternative modes of therapy. This attitude seemed to be the antithesis of enthusiasm regarding drug effects seen elsewhere. "Double-blind" studies of drug effects do not entirely preclude the communication of such attitudes, especially when "active drugs" are compared with relatively inert preparations.

We conclude that the social context within which pharmacotherapy is undertaken has importance in the over-all evaluation of therapeutic effect. It appeared as relevant as the specific pharmacological action of the drug and the psychodynamic meaning to the patient of receiving the drug. An attempt has been made to explore some of the im-

plications of these conclusions for evaluation of results in other psychiatric therapies.

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Neurophysiologic Effects of Electrically Induced Convulsions

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Numerous investigations have been made aimed at explaining the beneficial effects of electroshock therapy in certain psychiatric conditions, especially in depressed states. Although many hypotheses have been advanced,* studies on electroshock have been uniformly disappointing. Irreversible pathological effects have not been demonstrated after electroshock therapy.† The pathological changes which have been found with more intensive electroshock ‡ principally involve the vascular and perivascular structures. These changes, as pointed out by Ferraro and associates,[20] suggest an increased permeability of the blood vessel walls. Other studies have shown neurophysiologic and biochemical alterations, such as are known to occur transiently with convulsions,§ but have not clarified the relationship between electroshock therapy and the more prolonged benefit it affords in psychiatric conditions.

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* References 1 and 2.

† References 3-8.

‡ References 9-19.

§ References 21-27.

On the other hand, there is considerable clinical evidence to suggest that the therapeutic effectiveness of electroschock in psychiatric disorders may be due to the neuronal discharge of the convulsion per se rather than to any effects induced by the transmission of electric current through the brain. In view of this, and the relatively prolonged therapeutic effects of electroshock treatments, one is forced to consider the possibility that convulsions may produce changes beyond the known transient effects incident to the primary neuronal discharge and recovery of the seizure itself.

In a previous study,[28] relatively persistent neurophysiologic effects were found in the central nervous system secondary to an increase in the permeability of the blood-brain barrier as produced by cerebral concussion. Since the effect of either convulsions or current transmission on the cerebrovascular tree might be reflected in changes of the semipermeable characteristics of the cell membranes composing the blood vessel walls, the possibility of electroshock producing similar, prolonged neurophysiologic changes occurred to one of us (R. B. A.). The potentialities of the blood-brain barrier as a basic neurophysiologic mechanism capable of conditioning the central nervous system had been amply demonstrated to our satisfaction in previous studies.‖ Furthermore, the likelihood of cerebrovascular permeability effects being associated with electroshock therapy had been suggested, as already indicated, by some of the neuropathological studies following excessive electroshock. In addition, certain older studies,¶ although

‖ References 29-31.

¶ References 32 and 33.

utilizing techniques open to question, had suggested that permeability changes of the blood-brain barrier might be produced by epilepsy. With these points in mind, the present studies were initiated, utilizing techniques previously reported # for measuring alterations in the permeability of the blood-brain barrier.

METHODS

The studies involved determinations of the distribution of cocaine by spectrophotometric methods # in the brain and blood of cats after the intravenous administration of this drug in a control group and in a group of cats receiving a series of electrically induced convulsions.

Electrically Induced Convulsions.—A series of 12 electric shocks were given over a period of 22 days with the usual bifrontal placement of electrodes and with the use of an Offner electroshock apparatus delivering a current of 400 ma. for 0.2 second. Although this strength produced convulsions in most instances, slightly higher currents were used in a second shock, when necessary to induce convulsions.

Electroencephalograms. — Electroencephalograms were obtained on all cats with the use of a two-channel, Grass electroencephalographic apparatus. Four needle electrodes (24-gauge) were inserted in the frontal and parieto-occipital regions of the scalp on both sides after the hair had been closely clipped. Pentobarbital anesthesia (26 mg. per kilogram of body weight), injected intraperitoneally, gave adequate narcosis for the electroencephalographic phase of the study. Only cats with normal electroencephalograms were selected for the studies. Electroencephalograms were obtained after the 7th electrically induced convulsion and again three days after the 12th, and final, shock.

Cocaine-Distribution Studies.—Under moderate narcosis and in accordance with standardized techniques previously reported,[25] the final cocaine-distribution studies in both control and postshock cats were conducted after the intravenous administration of 15 mg. per kilogram of body weight of a 6% solution of cocaine hydrochloride. In the case of the postshock group, the cocaine studies were performed three days after the completion of

References 28 and 34.

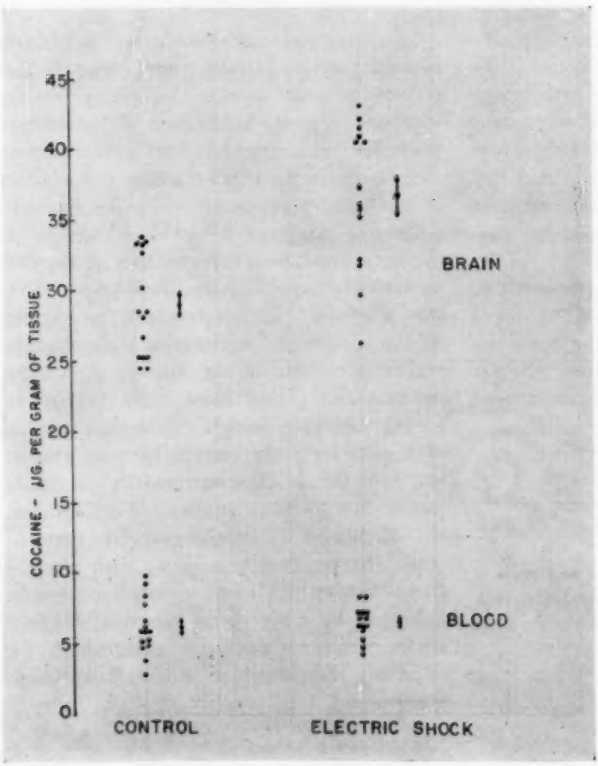

Fig. 1. — Spot graph showing the spread of experimental determinations, the mean values, and the standard deviations of the means on the distribution of cocaine hydrochloride in the blood and brain of cats under control conditions and three days after a series of electrically induced convulsions (see text).

TABLE 1.—*Spectrochemical Determination of Distribution of Cocaine Hydrochloride* in Blood and Brain of Cats Before and After a Series of Electrically Induced Convulsions*

Treatment	Experiment No.	Cocaine Level, γ/Gm. Blood	Brain
Control	1	5.3	28.4
(no electric shock)	2	6.0	32.7
	3	9.4	33.6
	4	7.8	24.6
	5	4.9	26.7
	6	6.6	24.6
	7	...	25.3
	8	9.8	25.4
	9	6.3	33.9
	10	6.0	30.2
	11	5.9	28.0
	12	5.2	33.6
	13	4.7	33.4
	14	2.7	25.4
	15	8.4	28.5
	16	3.8	....
After electric shock	1	7.3	35.7
	2	7.2	32.1
	3	8.4	35.2
	4	4.7	41.5
	5	4.2	37.3
	6	6.0	29.6
	7	6.9	40.6
	8	5.2	26.4
	9	8.3	40.6
	10	6.2	36.0
	11	7.3	40.9
	12	6.4	31.8
	13	6.9	42.1
	14	6.4	43.1

* Cocaine hydrochloride, 15 mg. per kilogram of body weight, injected intravenously, as described in the text.

the electroshock series of treatments. The cocaine was injected slowly and evenly over a 15-minute period, and at 5-minute intervals thereafter specimens of cerebrospinal fluid, brain, and blood were obtained and immediately frozen in carbon dioxide snow. The brain and blood specimens were extracted chemically by standardized methods and finally analyzed for cocaine by means of a spectrophotometric technique, utilizing a Beckman photoelectric spectrophotometer.

RESULTS

The results of the experiments are shown in Table 1 and are presented graphically in Figure 1. The analysis of the data (Table 2) includes the mean values, the standard deviations of the mean values, and tests for the significance of the difference of the means. The last values are expressed in the last column in terms of the odds against the difference being due to chance.

The validity of the significance test depends in part upon the supposition that the values included in the analysis are representative samples which follow the normal distribution law. The data, therefore, were subjected to a simple test capable of showing the nature of their statistical distribution. The approximation of the data to a straight line when plotted on probability paper indicated that they followed a normal distribution sufficiently closely to warrant the statistical testing of their significance. In addition, Student's *t*-distribution test gave results which were essentially the same as the standard deviation test for significance, as shown in Table 1.

The results indicate that a series of electrically induced convulsions in this group of animals produced a marked increase in the permeability of the blood-brain barrier and that this phenomenon persists over relatively prolonged periods. Whereas no measurable change in the concentration of cocaine appeared in the blood after a series of electrically induced convulsions, the brain values rose from $28.9\gamma \pm 0.9\gamma$ per gram of tissue, under control conditions (15 experiments),

TABLE 2.—*Summary of Statistical Analysis of Data on Distribution of Cocaine Hydrochloride* in Blood and Brain of Cats Before and After a Series of Electrically Induced Convulsions*

Specimen	Treatment	No. of Experiments	Mean Value of Cocaine, γ/Gm.	Standard Deviation	Significance Test	Odds†
Blood	Control (no electric shock)	15	6.2	0.5	0.7	1:1
	After electric shock	14	6.5	0.3		
Brain	Control (no electric shock)	15	28.9	0.9	4.6	2.5×10^5:1
	After electric shock	14	36.6	1.4		

* Cocaine hydrochloride, 15 mg. per kilogram of body weight, injected intravenously, as described in the text.
† Odds against results being due to chance.

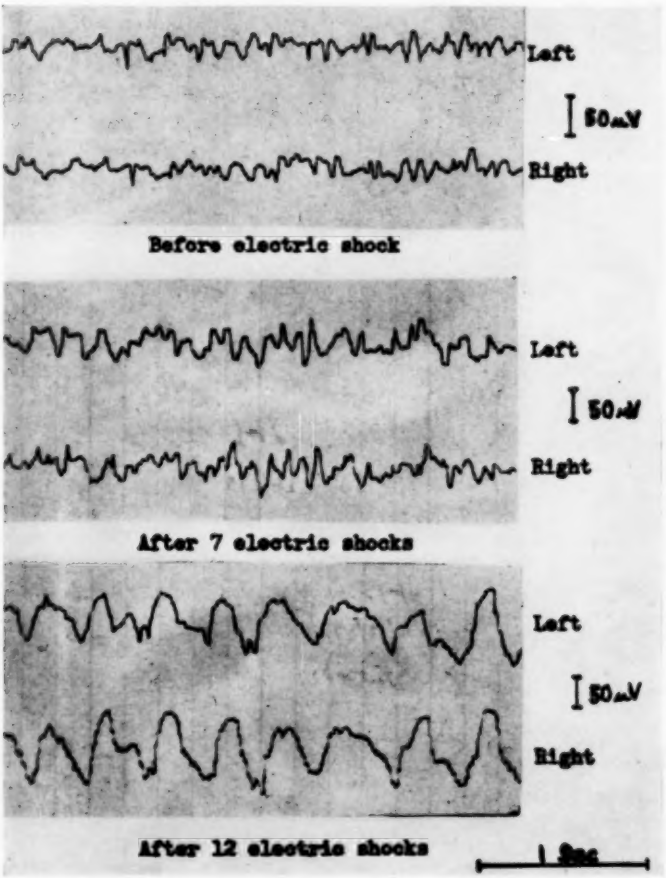

Fig. 2.—Typical electroencephalograms of Cat 15 before and after a series of electrically induced convulsions.

to $36.6\gamma \pm 1.4\gamma$ per gram of tissue, in 14 postshock experiments.

Representative electroencephalograms before and after the 7th and 12th electrically induced convulsions in cats are shown in Figure 2. In general, slight dysrhythmias were observed after the 7th convulsion and gross dysrhythmias were observed after the 12th convulsion.

COMMENT

*Neurophysiologic Studies on Electroshock.**—Variations in the technique of electroshock therapy have resulted in physiologic and biochemical differences which have permitted their relationship to the therapeutic effect of electroshock to be evaluated. Electroshock with curare has eliminated the majority of physiologic and biochemical changes associated with the peripheral, motor manifestations of convulsions.† Apnea, pronounced increases in venous pressure, and cerebral anoxia likewise have been ruled out.‡ Differences in nucleic acid metabolism and enzymes in the cerebrospinal fluid have been observed with different shock techniques,§ which have given more or less comparable therapeutic results. Again, no

* For a more complete review of the neurophysiologic studies on electroshock therapy and electrically induced convulsions, Gellhorn's text[1] should be consulted.

† References 35 and 36.

‡ References 37-39.

§ References 40-42.

correlation has been found between electroencephalographic alterations with electroshock therapy and therapeutic responses.‖ Likewise, differences in technique have resulted in clinical differences of memory disturbance, confusion, euphoria, and amnesia ¶ without corresponding differences in the therapeutic results obtained.

Numerous other changes have been observed after electroshock therapy, which also have been found to be transient effects and which, therefore, would not appear to correlate well with the more prolonged therapeutic effects of shock therapy. Other studies which suggest that electroshock therapy stimulates the sympatheticoadrenal system of the hypothalamus and thus modifies the hypothalamic-cortical balance affecting behavior patterns [1] are of great interest but, again, do not explain the prolonged effectiveness of this neurophysiologic procedure. With the purpose of ruling out such transient effects, the present investigation was so planned that the permeability studies were conducted three days following the last electroshock treatment. Previous studies [48] had suggested that permeability changes persist in some degree for much longer periods.

Permeability Effects of Electroshock.—Indirect electrical determinations (measurements of impedance) on the brain of experimental preparations subjected to all types of shock therapy # have shown more or less comparable increases in the permeability of the cell membranes of the brain. The authors have suggested that this mechanism may be related to the therapeutic effect of the shock procedures. The permeability effect observed by Spiegel and his co-workers persisted only for limited periods, however, and would not appear to correlate well with the more prolonged therapeutic effects of shock therapy.

As indicated previously, certain older studies have suggested that the convulsive state as seen clinically may increase the permeability of the blood-brain barrier.* More recently, the effect of electroshock therapy upon the permeability of the cerebrovascular tree has been confirmed by supravital dye studies on rabbits.[51] Trypan blue, which normally does not pass through the blood-brain barrier if administered intravenously, was found to stain the brain after repeated electrically induced convulsions. Unfortunately, the duration of these permeability effects was not determined. That this effect cannot be achieved after single or a limited number of electrically induced convulsions was suggested by the minimal electroencephalographic changes observed in our own study following seven electroshocks (Fig. 2).

In the present study a marked increase of permeability of the blood-brain barrier was found after a series of electrically induced convulsions, which persisted for relatively long periods. As mentioned previously, the present investigation was so planned that the permeability studies were conducted three days after the last electric shock, with the object of ruling out transient neurophysiologic effects. This was felt to be a crucial point and first requirement for the correlation of any neurophysiologic change, incident to electrically induced convulsions, with the relatively sustained clinical effects of electroshock therapy.

Pertinent to the question of whether the permeability effects of electroshock may be independently related to its clinical effects, however, is the old observation that electroshock therapy with subconvulsive or "petit mal" currents has little therapeutic value. It would be desirable to demonstrate whether proportional permeability effects occur with the administration of subconvulsive currents and other shock techniques, such as pentylenetetrazol (Metrazol) and insulin, which are known to produce beneficial therapeutic results. The present study suggests that significant and persistent permeability changes would not be produced with subconvulsive currents, since, as previously indicated, only slight electroencephalographic changes were found after seven successive electroshocks (Fig. 2). Nearly twice this number of elec-

‖ References 43 and 44.
¶ References 45-47.
# References 49 and 50.
* References 32 and 33.

troshocks were required to produce gross electroencephalographic changes and the marked and persistent permeability effects described in this study.

The concept of cerebral neurophysiologic conditioning (as evidenced by electroencephalography) secondary to cerebrovascular permeability changes is an attractive one in offering an explanation for persistent effects which might correlate with the clinical benefits of electroshock therapy. As indicated in the review of other known neurophysiologic effects, which have been found in the numerous studies on electroshock therapy, prolonged changes have not been noted which could be correlated satisfactorily with the clinical effects of this form of treatment. Furthermore, without benefit of pathological changes, it would appear difficult to explain such persistent effects in terms of known neurophysiologic mechanisms of primary neurogenic origin.

In summary, then, the value of the cerebrovascular permeability concept lies in the fact that (1) it involves a basic neurophysiologic mechanism capable of conditioning the neurophysiology of the central nervous system, (2) the present study suggests that this mechanism may be modified over relatively prolonged periods by electrically induced convulsions which might conceivably correlate with the somewhat sustained clinical effects observed after electroshock therapy, (3) other neurophysiologic changes have been found to be but transiently modified after electroshock, and (4) from what is known of neurophysiologic processes directly or primarily involving neuronal elements and pathways, persistent effects would not be anticipated.

The therapeutic effectiveness of electroshock therapy, however, cannot finally be related to cerebrovascular permeability except as this important neurophysiologic mechanism can be shown not to be present in significant and persistent form after subconvulsive doses of electroshock. The relationship would be even further strengthened if similar permeability changes could be demonstrate with pentylenetetrazol (Metrazol) and insulin shock.

SUMMARY AND CONCLUSIONS

Neurophysiologic studies, utilizing a modified spectrochemical technique for following the distribution of cocaine used as a tracer agent, have been performed on cats under control conditions and after a series of electroshocks. The object of these experiments was to determine whether or not alterations in the concentration of cocaine occurred in the central nervous system after a series of electrically induced convulsions. Significant and relatively persistent rises in the concentration of cocaine were found in the cerebral cortex after repeated electroshocks which induced convulsions. Since no change was observed in the concentration of cocaine in the blood of these same animals after electroshock, it was concluded that a series of electrically induced convulsions increased the permeability of the blood-brain barrier.

Gross changes in the electroencephalogram were observed to accompany the persistent change in the permeability, suggesting that cerebrovascular permeability may be important in the neurophysiologic conditioning of the brain.

The concept of cerebral neurophysiologic conditioning secondary to cerebrovascular permeability changes is discussed as possibly offering an explanation for persistent effects which might correlate with the clinical benefits of electroshock therapy. A review of the numerous other studies on electroshock therapy failed to show persistent neurophysiologic changes which could be correlated satisfactorily with the clinical effects of this form of therapy. The concept of cerebrovascular permeability is attractive in that (*a*) it involves a basic neurophysiologic mechanism capable of conditioning the neurophysiology of the central nervous system; (*b*) as demonstrated in the present study, this mechanism may be modified over relatively prolonged periods by electrically induced convulsions and hence might produce neurophysiologic effects that could be correlated with the somewhat sustained clinical benefits of electroshock

therapy, and (*c*) although neurophysiologic processes, directly or primarily involving neuronal elements and pathways, could scarcely be expected from what is known of them to produce persistent effects, the mechanism considered has the advantage of offering an explanation for a sustained conditioning of these elements without itself being dependent upon them.

This thesis, however, cannot be accepted without further correlative studies, as indicated.

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The Concept of Pseudofeeblemindedness

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In recent years, pseudofeeblemindedness, considered as either a clinical condition or a problem of differential diagnosis, has received increasing attention from workers in the field of the psychopathology of childhood. Apparently, more frequently than was the case in previous years, the clinician encounters conditions that he is unwilling to designate as "true" mental defect, even though, as the term "pseudofeeblemindedness" implies, these cases exhibit some of the characteristics of mental defect. Obviously, he must have in mind some concept of "true" mental defect which serves as a standard whereby he evaluates the individual case. Within this frame of reference, certain cases are judged to be not mentally defective. Among these cases, a certain proportion are further designated as being "pseudofeebleminded."

When one reflects on the situation, a number of questions raise themselves. One has to do with the exact meaning of the diagnosis of pseudofeeblemindedness. And, since the diagnosis depends basically upon the concept of "true" mental defect, one must also ask what is meant by "true" mental defect. The present paper deals with these questions. It attempts to analyze both the concept of pseudofeeblemindedness and that of "true" mental defect. As will be seen, this analysis suggests that the two concepts ought perhaps to be unified into a single broad concept of behavioral defect.

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PSEUDOFEEBLEMINDEDNESS AS FALSE DIAGNOSIS

We have first to distinguish between two meanings of "pseudofeeblemindedness." The term has been employed in two senses, which are in essence mutually exclusive and which require explicit differentiation. In one usage of the term, it represents a mistaken diagnosis; i. e., from the data at hand, a child is judged to be behaviorally retarded or deficient when in fact he is not. In its second usage, pseudofeeblemindedness denotes a condition of behavioral retardation or deficiency which is ascribable to factors other than those customarily held to be the essential antecedent conditions of "true" mental defect. In the first sense, pseudofeeblemindedness means a false inference regarding current behavioral status. In the second sense, it means a true inference which is accompanied, however, with the implication that unusual etiologic factors are responsible for the behavioral deficiency. The simultaneous use of the term in both senses (sometimes by the same author) has led to considerable confusion and misunderstanding.

The inference of mental defect is necessarily made on the basis of observation of a limited sample of behavior. Ordinarily it rests upon the evaluation of the patient's behavior in the interview situation, his performances in the psychological test situation, and the verbal reports of relatives, coupled with the results of physical examination. One measure of the validity of these procedures is the accuracy with which they predict the "true" behavioral status, i. e., the behavioral level generally characteristic of the patient in real life situations. The procedures are "valid" to the degree that a correlation exists between the behavior exhibited under the special conditions of observation provided by the interview or test (or that reported in the case history) and the behavior manifested

in daily life. Numerous extraneous factors may operate to affect the observed or reported behavior and thus to attenuate the correlation between these behaviors and actual life behavior. Such an attenuation in relationship results in inferences of less validity than would otherwise be possible.

Extraneous factors which may affect the nature of test or interview behavior are numerous and of a varied character. Temporary physical disability may go unrecognized while adversely affecting a child's behavior in an interview or the quality of his performance on a psychologic examination. Timidity, hostility, or distrust may have a similarly adverse effect upon the performances of adults as well as of children. Successful deliberate simulation of mental incompetence is probably not as rare as is usually assumed. The examiner himself constitutes an important variable. His skill and experience in eliciting optimal performance is often a decisive factor in affecting the validity of the findings, and his personal traits may be a significant determinant of the subject's performances. Those characteristics of the interaction between patient and examiner which are designated as "rapport" play an important role, particularly with younger children and emotionally disturbed patients.

Another source of invalid inference lies in the frequent utilization of inappropriate statistical norms in the interpretation of performance. An even more potent source of error is the employment of inappropriate procedures for the assessment of intelligence, e. g., verbal scales on children with speech or hearing deficits, performance tests on children with visual defects, etc. The information provided by persons concerned with the patient is also subject to distortions which may seriously affect the validity of inferences drawn from it. The retrospective reports of parents provide a type of data which has long been recognized as having only a moderate degree of credibility. The accuracy of descriptions of current behavior by teachers and social workers may be affected by attitudinal and motivational factors, particularly if the child is disturbing the classroom or family structure.

A false diagnosis of mental defect is most frequently made in the case of children who are showing delinquent or antisocial conduct. By definition, these children are behaving incompetently in a social sense. The basic question is, of course, whether a fundamental intellectual inadequacy is responsible for the social incompetence. In the absence of striking evidence to the contrary, the untrained observer is likely to consider that the question is already answered; i. e., he tends to confuse the lack of capacity for social adjustment with intellectual inadequacy. In addition, the conviction on the part of the social or educational authorities that a child should be institutionalized may play a role in presenting a bleaker picture of the intellectual aspects of his behavior than is actually warranted. On the child's part, hostility and distrust may so constrict his behavior in the interview and test situations that over-all efficiency of performance in these diagnostic situations is that of a mental defective. If he is in difficulty with the law, an element of simulation may enter the picture.

It is not difficult to understand how a false inference of mental defect, i. e., that a child is socially incompetent by reason of intellectual subnormality when in fact he is not, might be made on the basis of observational data and evaluations such as have been described. Acceptance at face value of the verbal reports of informants and an uncritical interpretation of performance in diagnostic situations without consideration of the possible influence of distorting factors might lead, in any given case, to a diagnosis of mental deficiency, when in reality the child's social incompetence is determined by motivational and attitudinal factors rather than by intellectual inadequacy.

If such an erroneous diagnosis is made and if, in later years, the person's behavior and achievements show clearly that he does not suffer from significant intellectual inadequacy, a review of his case may lead to

the conclusion that the original inference was false; i. e., he never was intellectually subnormal. The presumption is, then, that the initial diagnosis was based on inadequate data or on a faulty interpretation of the available data. His behavior suggested mental defect, but fuller or more critical examination would have disclosed the patient's intellectual adequacy. Because the patient gave the impression of being mentally defective, such an erroneous diagnosis is often referred to as pseudofeeblemindedness.

In my opinion it is difficult to justify such a designation for what is essentially an error in diagnosis. Certainly, it would seem better to keep the focus of attention on the responsible clinician rather than to project it, so to speak, on the patient. Errors in diagnosis ought not to be given the status of a clinical entity, and it is reasonable to conclude that in the first sense of the term there is no such thing as "pseudofeeblemindedness."

PSEUDOFEEBLEMINDEDNESS AS MENTAL DEFICIENCY OF ATYPICAL ETIOLOGY

The second sense in which the term "pseudofeeblemindedness" is employed presents a quite different situation. It rests upon the conception that "true" mental defect implies the operation of certain etiologic factors. If it can be assumed that defect or disease of certain critical cerebral areas is at least the proximate cause of "true" mental deficiency, then, in contrast, pseudofeeblemindedness presents a picture of behavioral retardation which is virtually identical with that associated with "true" mental deficiency but which is determined by other factors, most (but not all) of which are extracerebral in nature. Thus, the distinction between "true feeblemindedness" and "pseudofeeblemindedness" depends upon the nature of the responsible etiologic factors. Pseudofeeblemindedness may be said to represent mental deficiency of atypical etiology.

This atypical etiology may be classified into a number of broad classes of determinants: (1) sensory deprivation, such as visual or auditory handicap; (2) motor deficit, as in cerebral palsy; (3) cultural deprivation, as respresented by a nonstimulating social or family environment and inadequate schooling; (4) emotional disturbance, which is conceived as exerting an inhibitory effect on intellectual function and, consequently, on the acquisition of basic mental abilities.

It is generally appreciated that each of these classes of factors is capable of exercising a depressing effect of at least a moderate degree on intellectual level, and it is not difficult to construct a theoretical model, illustrating how retardation in the acquisition of the numerous intellectual skills subsumed under the global valuistic concept of "intelligence" can result from the operation of one or another factor. The general tenor of empirical findings which show moderate retardation in intelligence to be characteristic of groups of handicapped children, such as the blind, the deaf, and the culturally underprivileged, also supports this formulation. As a consequence, the experienced examiner, when he evaluates the performances of a handicapped child, tends to take account of the general finding of a moderate retardation being characteristic of the group to which the child belongs. He is also careful to base his evaluation on procedures requiring performances which are well within the behavior repertory of the child, e. g., visual rather than auditory tests to the hard of hearing child, performance rather than verbal tests to the culturally handicapped child, etc. His interpretation of the performances of the child is likely to be rather "liberal," and the finding of a moderate retardation in intellectual development in such a child, e. g., an intelligence quotient of 80-85, is usually interpreted as presumptive evidence that the child's intelligence is within normal limits.

However, the examiner can hardly afford to be too "liberal" in his evaluation. He knows that the typical effect of physical or social handicap is only a relatively slight depression in intelligence level. He also knows that these handicaps tend to be correlated with the occurrence of mental deficiency. Therefore, if a handicapped child's

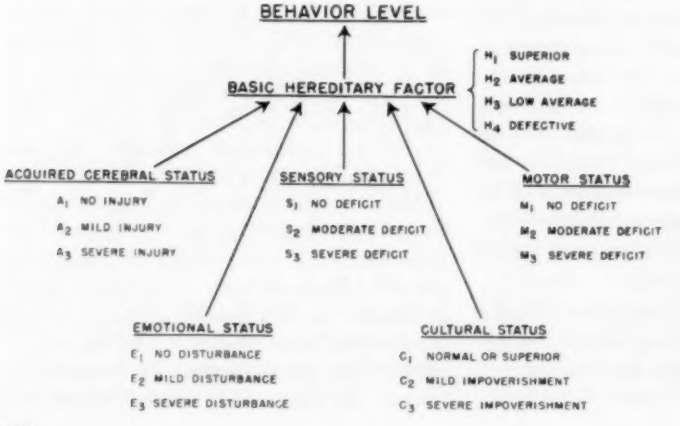
performance is definitely below normal limits, e. g., below an intelligence quotient of 80, the retardation in intellectual development cannot reasonably be ascribed to the typical operation of a physical or social handicap. If, then, the totality of data is consistent in presenting a picture of significant behavioral retardation, the diagnostic inference of mental deficiency must be made.

Theoretically, two distinct sets of factors may be operating to produce the observed behavioral deficiency in such a case. The first possibility is that we are dealing with a "true" mental deficiency; i. e., the cerebral defect or disease which is customarily held to be responsible for states of mental deficiency is present. The physical or social handicap is either an incidental accompaniment of the mental deficiency, or, in the case of physical handicap, it may point to a global developmental disturbance, of which both the behavioral deficiency and the physical deficit are part expressions. In either case, the handicap per se is not a significant determinant of the mental deficiency.

The second possibility is that we are dealing with a case of pseudofeeblemindedness, that is, with an atypically severe effect of the physical or social handicap. The reasons why a handicap should have particularly severe depressive effects on behavioral development in the case of one child and not in the case of another are not well understood. However, clinical experience does suggest that a particularly deleterious effect may occur when a handicap affects a child whose intellectual potentialities are rather limited to start with or when combinations of handicaps are present. One might think in terms of an hereditary core with respect to intellectual potential, varying from individual to individual, through which various factors—cerebral status, sensory status, motor status, emotional status, and cultural status—operate to produce a behavior resultant. This conception is illustrated in the accompanying Figure.

As outlined in the Figure, "Behavioral Level" is conceived to be the resultant of a number of determining factors. A prime determinant is the variable designated as the "Basic Hereditary Factor." This is a continuous variable which, for practical purposes, might be subdivided into four levels, as indicated. The defective level, H_4, can be assumed to account for mental deficiency of a purely hereditary character. Other factors being held constant, the other levels, viz., H_1, H_2, and H_3, would account for variations in the intelligence quotient within the normal and superior ranges, e. g., 80-150.

This hereditary factor has a double significance. Not only is it a potent determinant in its own right, but it also serves the function of "host," so to speak, for the other factors. That is to say, the other deter-



Theoretical schema illustrating interaction of determinants of mental deficiency and pseudofeeblemindedness.

minants—Acquired Cerebral Status, Sensory Function, Motor Function, etc.—operate through the medium of the nuclear factor of hereditary status, interacting with it to produce their effects.

With respect to the factor of acquired cerebral status, I have in mind the occurrence of brain injury or disease of all degrees of severity. Severe insult suffered in early life (H_3) would account for the category of purely exogenous mental defect. Moreover, a relatively poor, but not defective, hereditary status, as represented by level H_3, combined with mild injury, as represented by level A_2, might produce high-grade mental deficiency, when neither factor acting alone would produce it, leading to what might be called "mixed" mental defect. Thus, we have the combination H_3A_2 as an adequate determinant of high-grade mental deficiency. A good many institutionalized cases seem to fall in this category, perhaps as many as fall in either of the "pure" categories.

Turning to the defect states of presumably atypical etiology, the conditions of pseudofeeblemindedness, the determining factors of sensory function (S), motor function (M), emotional status (E), and cultural status (C) will be noted. Each is a continuous variable, which, for convenience, has been analyzed into three levels: (1) no defect, (2) moderate defect, and (3) severe defect. As has already been mentioned, empirical data on the blind, the deaf, and the culturally underprivileged indicate that, while the handicap involved does lead to some retardation in behavioral development, mental deficiency is not the typical outcome. Since these are group results, it may be assumed that the typical outcome holds for an average hereditary status, i. e., H_2. What these clinical findings can be interpreted to mean is that the interaction of defective sensory or motor function, emotional disturbance, or cultural handicap with an average hereditary status does not lead to mental defect; i. e., such combinations as H_2S_3, H_2M_3, or H_2C_3 are *not* determinants of mental defect. However, if one considers the possibility of an interaction between, for example, defective sensory or motor function with a low-average hereditary status, that is, an H_3S_3 or H_3M_3 combination, it is conceivable that such an interaction could lead to high-grade mental defect. Indeed, it seems rather probable that it would. In concrete terms, the conception is that while a child with average or superior endowment might, with proper educational guidance, overcome the handicap of deafness or cerebral palsy and attain an intellectual efficiency which is within normal limits, the same sensory or motor handicap would lead to a mental defect state of moderate degree in a child of low- or dull-average intellectual endowment.

To take another example, the factor of severe cultural impoverishment does not usually lead to mental deficiency. The typical resultant is a low- or dull-average intellectual level; i. e., the combination H_2C_3 does not lead to mental defect. But what of the combination H_3C_3? Can the child of low-average endowment overcome the handicap? It is distinctly possible that he might suffer a sufficiently serious retardation in intellectual growth as to make him a borderline or moron-level mental defective. One suspects that a good many cases of so-called familial mental defect actually belong in this category rather than in the purely hereditary category.

All these situations represent theoretical examples of pseudofeeblemindedness, the general formula being the interaction of a specific handicap with a subnormal (but not defective) hereditary endowment. One speaks of the inability of the child to overcome the deleterious behavioral effects of the sensory, motor cultural, or emotional handicap. This inability might be permanent, or it might be temporary; i. e., over a period of time, the developing person might be able to overcome the more significant effects of the handicap. Under these conditions, one would have the situation of a person who is mentally defective as a child but who, gradually, through the adolescent years gains enough in behavioral efficiency so that he is no longer classifiable as a mental defective.

In addition to the interaction of a specific deficit with a subnormal hereditary endow-

ment as a determinant of mental defect, there is the possibility that combinations of special defects themselves will produce mental defect even in a child of average intellectual potentialities. Deafness combined with cultural impoverishment or blindness combined with motor deficit might constitute sufficiently severe handicaps as to cause a gross retardation in behavioral development.

It must be emphasized that there is nothing false or unreal about these intellectual defect states, even though they may be called "pseudofeeblemindedness." They are true mental defect states from the behavioral standpoint, differing from the more conventional types of mental deficiency only in respect to etiology. Nor is there necessarily an impermanent quality to these conditions. They can continue without alleviation throughout life, in much the same manner as untreated cretinism.

While this conception of physical, psychological, and social handicap causing mental deficiency in a child seems clear enough theoretically, in practice it is not easy to distinguish between such a state of affairs and that represented by the coincidental occurrence of the handicap with so-called "true" mental defect. Limitations in knowledge, as well as lack of precision in psychodiagnostic methods, make it quite difficult to differentiate between the two conditions. At the time of initial examination, the diagnostic inference is more likely to be that one is dealing with a coincidence of the mental defect state and the handicap than with a condition of pseudofeeblemindedness. The first inference often seems to the clinician to be the more "parsimonious" one. Actually, it does not involve fewer assumptions than does the inference of mental deficiency on the basis of the handicap. However, it does involve more conventional (hence, more acceptable) assumptions and therefore appears easier to make. The diagnosis of pseudofeeblemindedness is more likely to be made only after a period of time has elapsed during which the course of the handicapped patient's development has been such as to show clearly that the diagnosis of mental deficiency is no longer tenable. In short, an impermanent pseudofeeblemindedness is more readily diagnosed than a permanent one. But this cannot be taken to mean that permanent conditions of pseudofeeblemindedness do not exist.

CONCEPT OF "TRUE" MENTAL DEFICIENCY

In order to understand the meaning of pseudofeeblemindedness and to assess its place in clinical thinking, it is necessary to review the notion of mental deficiency itself. It is not at all a simple concept. On the contrary, it is a rather complex one, which possesses behavioral, etiologic, developmental, and prognostic implications. It is also evident that the concept does not mean quite the same thing to different people. With respect to each of these aspects, one finds considerable disagreement among workers in the field.

This is true even with respect to the intellectual aspect. Most students regard the proposition that the cardinal behavioral feature of mental deficiency is intellectual subnormality as virtually axiomatic. Nevertheless, as eminent an authority as Tredgold [1] would not admit this and would insist that the nuclear manifestation of mental deficiency is a defect in behavioral adaptability, which may or may not be accompanied by intellectual subnormality. Similarly, Delay, Pichot, and Perse [2] have advanced the notion of "camouflaged mental deficiency," as they call it, i.e., social incompetence, camouflaged by a good intelligence quotient.

However, the issues of etiology and prognosis are decidedly more important. With regard to etiology, it is reasonable to state that some concept of defect or disease of critical cerebral areas is what most clinicians have in mind when they think of at least the proximate cause of mental deficiency, whether the defect state be of a hereditary or an acquired nature. Thus, Tredgold writes that "the brain is the organ for the manifestations of mind . . . the material basis of mental deficiency consists in an inadequate development, or persistent imperfection of function, of the neurones of the mantle of

the brain . . . primary amentia is the result of an inherent capacity of these neurones to attain an adequate degree of development and function, while secondary amentia is due to their development having been arrested by some external cause." *

In evaluating this statement by Tredgold, it is useful to consider separately the neuropathologic findings in low-grade deficiency as contrasted with high-grade deficiency, since the general picture seems to be different in these two broad groups. In low-grade deficiency, positive neuropathologic findings, while apparently not demonstrable in every single case, seem to be the rule.† However, a somewhat different picture is encountered in high-grade defect. Positive neuropathologic findings are *not* the rule. On the other hand, it would be inaccurate to conclude that negative findings *are* the rule. It appears that the neuropathologic picture is simply unpredictable. In many cases the findings are a normal anatomy and histology. Tredgold, who cannot be accused of being overly skeptical about the assumption of a neuropathologic basis for the high-grade defect, summarizes the situation as follows:

> In general, the brains of the milder aments are a little less in size and weight than the normal, and their convolutions tend to be wider and simpler; but they rarely present any of the gross abnormalities which characterize those of lower grade. Further, microscopical examinations do not show the marked paucity and imperfection of neurones which occur in idiots and imbeciles, and with our present methods of investigation the brains of many high-grade feebleminded individuals would pass muster as normal.‡

Thus, it is probably fair to say that there is a lack of convincing evidence of a consistent neuropathologic basis for high-grade mental deficiency. There are two possible interpretations for this state of affairs. The first is that these negative, or at least inconsistent, findings are a consequence of limitations in our present methods of laboratory investigation. The second interpretation holds that we must accept the facts as they are and that, in any case, it is not necessary to assume that all mental defect necessarily rests on cerebral defect. The idea that neurosis and psychosis are necessarily based on cerebral disease or maldevelopment has long been abandoned. There is no reason to hold to it in the case of high-grade mental defect.

Tredgold's assertion that high-grade mental defect is always based upon cerebral defect or pathology, which is often not demonstrable, is a statement of faith. One may or may not accept this statement of faith. If one does not, one looks to other determinants of the defect state, i. e., determinants other than demonstrable cerebral pathology. When one does this, one moves into the area of pseudofeeblemindedness.

PROGNOSIS IN MENTAL DEFICIENCY

The question of the ultimate fate of persons who, in childhood, show the behavioral symptom complex of mental deficiency has occupied investigators for half a century. However, before reviewing the findings and discussing the implications of these studies, it is necessary to consider a point of view which, in a sense, "eliminates" the problem of prognosis by establishing a poor prognosis as one of the essential characteristics of this behavioral disorder.

For some workers, the concept of mental deficiency is defined not only by etiologic factors and behavioral manifestations but also by the course and outcome of the disorder. For example, Doll,[6] in his formulation of an "inclusive concept" of mental deficiency, lists as an essential criterion for the diagnosis the condition that the behavioral defect must obtain at maturity. Thus, he states that "the concept of the essential incurability of feeble-mindedness is part of the diagnostic picture. If the prognosis suggests a possibility of amelioration of symptoms amounting to prospects of ultimate normality, then a diagnosis of mental deficiency is not warranted." §

Nevertheless, while it is true that at the present time a poor prognosis is characteristic of virtually all cases of lower-grade defect

* Reference 1, pp. 106-107.

† References 1, 3, 4, and 5.

‡ Reference 1, p. 121.

§ Reference 6, p. 423.

and of the majority of cases of higher-grade defect, most workers in the field, however conservative their expectations in regard to prognosis may be, probably would not include the idea of a fixed outcome as an essential part of the concept of mental deficiency. Instead, they would prefer to rely on etiologic and behavioral criteria to establish the diagnosis and to make the question of outcome a matter for empirical investigation and for possible modification.

There are sound reasons for this refusal to include outcome as an *essential* part of any diagnosis, however important it may be in the *description* of a disease or condition. This holds true even in such instances where an empirical relation has been so securely established that at the present time the diagnosis does in fact predict the terminal state with a high degree of accuracy. The fundamental objection to such a procedure derives from the fact that the course and outcome of a disease are not solely a characteristic of the disease itself but are also a function of the efficiency of medical, psychologic, and educational practice at any given time. In other words, course and outcome depend upon the prevailing level of technologic efficiency. Since this efficiency level changes with time, a diagnostic concept which is based on course and outcome can hardly have a firm foundation.

This idea of poor prognosis as an integral part of the concept of mental deficiency appears to represent an application of the old doctrine of "malignancy," characteristic of a bygone era of medicine, when the physician, lacking a knowledge of pathology and possessing only the most meager therapeutic resources, could claim distinction solely on the basis of his ability to prognosticate. As pathologic anatomy and physiology developed during the 19th century, this notion of "malignancy," i. e., of a poor outcome being inherently characteristic of a disease and therefore essential for its diagnosis, was abandoned in most fields of medicine. Apparently, it lingered in psychiatry until at least the early years of the 20th century. When Kraepelin made his great diagnostic synthesis of catatonia, hebephrenia, and other symptom pictures into the single category of dementia praecox, he included a typical course and outcome as essential features of the disorder. But these were precisely the aspects of his conception that encountered the most significant resistance among his contemporaries, and it was not many years before these elements of the diagnosis succumbed to Bleuler's formulation, which explicitly excluded course and outcome as necessary features of the disease.

The notion of "malignancy" plays little role in current neuropsychiatric thinking. This is not to say, of course, that a diagnosis may not have prognostic implications but says only that such implications do not serve as the essential basis for the diagnosis. They follow, rather than precede, the diagnosis. For example, the diagnosis of schizophrenia depends upon evaluation of a patient's present and past behavior. Once the diagnosis is established, it is not dependent upon the vicissitudes of the course or the response to treatment. Thus, it is not generally held, because a patient responded favorably to insulin, electroshock, frontal leucotomy, or some other treatment, that he was not "really" schizophrenic, that he was a "pseudoschizophrenic", or that his behavior merely "simulated" schizophrenia.

But this is precisely the type of reasoning that is often applied to cases of mental deficiency which do not follow the "prescribed" course. Thus, when follow-up study indicates that a patient, diagnosed in earlier years as mentally deficient, is socially competent and shows no more than minimal intellectual retardation, a *post hoc* judgment is made that the initial diagnosis was false, i. e., the patient was "pseudofeebleminded." This judgment is often accompanied by the suggestion that had a more careful initial examination been done, the original diagnosis would not have been made. However, the procedures which would have made the examination more careful, or the criteria necessary for a differential diagnosis between "true" and "false" feeblemindedness, are seldom specified.

It is probably fair to state that the majority of workers reject such *post hoc* reasoning. The diagnosis of mental deficiency cannot depend upon a patient's status 10 years later. His future status is a matter for empirical investigation and analysis.

In considering the ultimate status of persons who in childhood were diagnosed as mentally defective, it is desirable to consider the lower and higher grades separately, for, as in the case with the neuropathologic aspects, the two levels present rather different pictures. In the case of low-grade defect, follow-up study may or may not disclose significant changes in the intelligence quotient. However, even if a large change has occurred, it usually has no decisively important implications for the basic issue of social competence. Thus, a change in the intelligence quotient from 35 to 55 or 60 may be recorded, but one finds that the patient is still mentally defective, the only shift being in the category of defect.

Follow-up studies of higher-grade defectives have yielded more interesting results.|| Some of these studies date back many years. All of them are in accord in finding that a significant proportion of persons who, in childhood, were diagnosed as mentally defective and who were treated as such(i. e., were institutionalized or placed in special classes) prove to be socially competent adults. This proportion varies from one-sixth to one-fourth, depending upon the criteria of the investigator and his particular sample of cases. The socioeconomic adjustment of these subjects is found to be variable, ranging from marginal to high-average. Their intelligence test performances vary from borderline to high-average. Their typical socioeconomic adjustment and intelligence test rating can perhaps best be designated as dull-average.

Thus, these studies indicate that some patients appear to show an alleviation of their mental defect state as they reach maturity, their improvement being reflected in a rise in the intelligence quotient and in socioeconomic competence. The reasons for this change in status are unknown, but, whatever be the determinants, the facts are incontestable.

|| References 7 through 12.

CONCLUSIONS

In summary, we find that in a proportion of cases of high-grade mental deficiency it is not possible to demonstrate a neuropathologic basis. Further, a proportion of cases of mental deficiency prove to be of a temporary nature. Such cases sound suspiciously like those which have been designated as "pseudofeebleminded," in that, by definition, the case of pseudofeeblemindedness lacks the neuropathologic condition responsible for so-called "true" mental defect and, in practice, pseudofeeblemindedness is usually diagnosed when a change in status has occurred, that is, when it exists as a temporary condition. However, we do not know that these cases represent pseudofeeblemindedness in the explicit sense in which I have described the condition, i. e., mental defect of atypical etiology. It is possible that we are dealing with erroneous initial diagnoses, i. e., pseudofeeblemindedness in the first sense of the term, as discussed in this paper. But there is no evidence for this supposition, either. It seems clear that there are a not inconsiderable number of cases with a diagnosis of mental deficiency in childhood which do not square with traditional notions about the etiology and prognosis of this group of disorders. On the other hand, the distinction between such cases and those in which the condition might be designated as pseudofeeblemindedness is not at all clear.

The implications of these findings are that traditional concepts of mental deficiency, to the degree that they include a specific etiology, neuropathologic basis, or course as defining terms, should be abandoned. A broader formulation, such as that recently proposed by Benda,[3] which calls for a reexamination of the relations between mental "deficiency" and mental "illness" and which reopens the general question of etiology, appears to be more adequate. Since we deal with symptom pictures of multiple etiology, no one specific etiology has any claim to

precedence over any other as being the primary antecedent condition of so-called "true" mental deficiency. All cases are examples of "true" defect, by behavioral criteria. Conditions of "pseudofeeblemindedness" can be conceived as being "true" defect states with certain types of etiologic background. Because of their clinical importance, detailed study of the pathogenesis of these conditions is strongly indicated.

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Autonomic Pharmacology in Schizophrenia

Review of the Literature and Report of Preliminary Investigations

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I. BLOOD PRESSURE RESPONSES TO PRESSOR AND DEPRESSOR AGENTS AND THEIR INHIBITORS

The search for evidence for and against autonomic dysfunction in schizophrenia constitutes a large portion of the physiological-metabolic literature of the disease. Because of the concomitant clinical signs of autonomic disturbance,[22] such as hypotension, variability of pulse rate, acrocyanosis, pupillary irregularities, excessive salivation, and disordered gastrointestinal regulation, numerous investigators have sought to implicate, or exonerate, the autonomic nervous system in the pathogenesis and differential diagnosis of schizophrenia. Of the several tests which have been employed to study autonomic function,* those most widely utilized, if at times erroneously, have involved the administration of drugs known to act on the same organs as does the autonomic nervous system. Because of their ready determinability, blood pressure changes have been extensively studied as an index of autonomic response, and will be used in the present study.

The utilization of autonomic drugs for study of the autonomic nervous system has been criticized on several grounds. It is argued that they are used in grossly nonphysiological quantities, and for only brief intervals of time. Furthermore, Altschule [21] points out that changes following their administration do not indicate involvement of the autonomic nervous system, but, rather, may result from the reactivity of the end-organs upon which they work and/or the potency of the enzymes (e. g., cholinesterase) which inactivate them. In reply to the first criticism, it must be remembered that much of our present knowledge of the autonomic nervous system is directly attributable to Langley,[23] who used an autonomic drug (nicotine) as a means of study. To reply to the second criticism is not as easy. However, it is well known that a disturbance in the autonomic nervous system proper can produce an apparent disturbance in the end-organs (e. g., the superreactivity of denervated structures [24]). Thus, it is not impossible that, as an example, slightly diminished reactivity of the end-organs may indicate slightly altered function within the autonomic nervous system. Furthermore, Gellhorn [35] has offered strong evidence for consideration of the role of reflex changes (which certainly involve the autonomic nervous system) following drug administration. In an attempt to evaluate the reactivity of the end-organs (i. e., the smooth muscle in the skin and splanchnic vessels, and cardiac muscle) in schizophrenia, the present study was undertaken. In an additional attempt to elicit differences between the reactivity of the cardiovascular system of schizophrenics and that of nonschizophrenics, blocking agents, which are believed to act on the same sites in the effector organs as do the stimulating agents,† were employed. The vasopressor and depressor agents used are synthetic *l*-epinephrine and methacholine (Mecholyl); the respective antagonists administered are phentolamine (Regitine ‡) and atropine.

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Dr. Kline assisted with the experimental design and the administration of medication. Credit otherwise belongs to Mr. Silverstein.

* References 14 and 20.

† Goodman and Gilman,[24] p. 413.

‡ Regitine was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J., and is discussed in Part II.

REVIEW OF THE LITERATURE

As with most physiological studies of schizophrenics, a variety of responses to injected epinephrine have been reported by different investigators. These are summarized in Table 1.

If to the 10 studies which found a major difference in the pressor response between schizophrenics and nonschizophrenics are added 6 more (4 cited by Langfeldt [8] and 2 by Lowrey and Wright [2]); and to the 9 studies which found no significant differences are added 2 more (again cited by Langfeldt [8]), it would appear that 16 investigators have shown a disturbance (a diminished reactivity, in all cases) in the schizophrenic response to epinephrine, while 11 have reported no difference from the nonschizophrenic response. The explanation for such discrepancies is not immediately apparent. As Table 1 indicates, they cannot be explained by the method of administration or the dosage of the drug. They may, however, reflect differences in the pharmacological agent used. Most commercial products of epinephrine contain varying quantities of arterenol (nor-epinephrine), and, as is well known, the cardiovascular effects of the two drugs differ widely.[25] Unfortunately, only a few of the investigators cited indicated the exact preparation used. Other possible explanations for the reported inconsistencies include differences in the timing of measurements and in what actually is measured (i. e., the intensity, latency, or duration of the response); utilization of other investigators' controls; poor utilization or nonutilization of statistical analysis, and, of course, the tremendous heterogeneity recognized in schizophrenic samples.

An interesting observation, and one on which there is somewhat more agreement, but one which still requires further investigation, is the reported diminution of the pressor response in catatonia, especially in catatonic stupor.§

The literature of the action of vasodepressor drugs is also subject to repeated inconsistency. Thus, several observers ‖ have reported greatly increased reactions to pilocarpine in schizophrenics; others have noted diminished responses,¶ normal responses,# or responses which vary with the type of schizophrenia.[8] Likewise, increased,* diminished,† and normal ‡ responses have been observed following methacholine. One study [18] found no differences with carbachol.

The literature concerning the use of blocking agents in schizophrenia is presented in Part II.

MATERIALS AND METHODS

Since faulty technique has been mentioned as one possible explanation for the conflicting results cited above, the methods of the present study will be given in detail.

The schizophrenic group consisted of 11 patients who are part of a larger group being studied extensively by the Rockland State Hospital Research Facility. To qualify as research patients,[21] all satisfied the following criteria: All were adult men under 45 years of age; all had been hospitalized for more than 10 years and had been past the age of 16 when first admitted. All were examined by five qualified psychiatrists, who agreed on the diagnosis of schizophrenia. All had normal physical examinations, a record of maintained good physical health while a patient, and no abnormalities reported in complete blood count, urinalysis, liver chemistries,§ sedimentation rate, and chest x-ray. The group included all diagnostic types, and about one-half showed evidences of marked deterioration. No patient on any form of somatic, including pharmacological, therapy was used. The control group consisted of eight employees of Rockland State Hospital (attendants, technicians, occupational therapists, and a chemist), all of whom had been employed for at least one year, were in good physical health, and had never been hospitalized for mental illness. Unfortunately, a definite bias may exist in the ages of the two groups. The mean age of the schizophrenics was 40.8 years, with a high of 42 and a

§ References 1, 7, 8, 11, 14, and 17.

‖ References 8 and 26. Grinevic, C., and others, cited by Sachs.[14]

¶ References 7 and 8.

References 10, 11, and 14.

* References 17 and 30.

† References 18 and 27.

‡ References 19, 28, and 29.

§ The normalcy of these chemistries is to be stressed, in view of the reported disturbance in cholinesterase (and possibly other enzymatic) activity which occurs with impaired hepatic function.[62]

TABLE 1.—*Summary of the Reported Effects of Epinephrine on Blood Pressure in Schizophrenia*

Author, Year	Preparation	Route of Administration	Dose, Mg.	No. of Subjects: Schiz.	No. of Subjects: Controls	Observations	Authors' Conclusions
Schmidt [1] 1914	"Adrenalin"	S. C.	..	34	36	Schiz. systolic rise less than 15-18 mm. Hg; control rise 40-80 mm. Hg	Schiz. insensitive
Lowrey & Wright [2] 1920	"Adrenalin"	S. C.	1	60	18	20 schizophrenics & 4 controls had fall in systolic pressure	No difference
Newcomer [3] 1922	"Adrenalin"	I. V.	..	5	8	.....	No difference
Raphael [4] 1923	"Epinephrin"	S. C.	1	56	..	.....	Less response in acute schizophrenia
Stuurman [5] 1924	"Epinephrin"	S. C.	0.7	..	..	.....	Schizophrenics show diminished response
McWilliam [6] 1925	"Adrenalin"	S. C.	0.5	..	..	.....	Schizophrenics give very slight reaction as compared with others
Claude [7] 1926	"Suprarenal"	.....	..	..	..	.....	Nonparanoid schizophrenics show no change—"irreducible atony"
Langfeldt [8] 1926	"Adrenalin"	I. V.	0.01	40	7	Schiz. mean †=29.5 mm.; control mean, 11.1 mm.; 11 schizophrenics showed fall in systolic pressure	Diminished response in catatonics; otherwise no difference
Kanner [9] 1928	"Adrenalin"	S. C.	1	34	9	Schiz. mean=2.8 mm.; control mean, 29.1 mm.	Schizophrenics show greatly diminished response
Northcote [10] 1929	"Adrenalin"	I. V.	0.01	50	..	18 schizophrenics showed fall in systolic pressure	No characteristic response
Northcote [11] 1932	"Adrenalin"	I. V.	0.005	16	..	.....	No characteristic response; catatonics slightly less responsive
Hoskins & Jellinek [12] 1933	"Adrenin"	.....	..	92	..	Schiz. mean, 78% of control mean	Great variation in schizophrenics, but less responsive
Freeman & Carmichael [13] 1935	"Epinephrin"	I. V.	0.05	72	24	Schiz. mean=43.8 mm.; control mean, 56.2 mm.; schizophrenics tend to show fall in diastolic pressure	Schizophrenics less responsive, more variable
Sachs [14] 1936	"Adrenalin"	S. C.	1	100	..	40 schizophrenics showed no response; 34 schizophrenics, hypernormal response; 7, hyponormal response; 15 expected normal response	Catatonics slightly less responsive, otherwise nothing characteristic
Dynes & Tod [15] 1940	"Adrenalin"	I. M.	5	19	6	Schiz. mean=14 mm.; control mean, 15 mm.	Schizophrenics have wider range and variability, show less emotion; otherwise similar
			1	10	6	Schiz. mean=23 mm.; control mean, 29 mm.	
Freeman [16] 1943	"Epinephrine Hydrochloride"	I. M.	0.01 mg./kg.	32	20	Schiz. mean=12.1 mm.; control mean, 19.8 mm.	Schizophrenics show diminished reactivity
Funkenstein [17] 1949	Synthetic /-epinephrine	I. V.	0.05	37	78	20 schizophrenics sole members of group showing least response	Schizophrenics show greater variability, take longer for homeostasis to occur; most schizophrenics show small response; can predict prognosis by type of response
Shurley & Morris [18] 1951	Epinephrine chloride	I. V.	0.1	8	12	.....	Schizophrenics show small systolic rise; approximates control after insulin
Glaser [19] 1952	"Epinephrine"	I. V.	0.05	42	20	Paranoid mean 63 mm.; hebephrenic catatonic mean 56 mm.; control mean 54 mm.	Schizophrenics react normally; somewhat more reactivity after topectomy

* Cited by Trentzch.[5]
† Mean of maximal systolic change.

low of 39 years. The control mean age was 31.3 (high of 40, and low of 22). In view of the reported effect of age on parasympathetic tone,‖ the possibility of significant differences of age between the groups must be borne in mind in evaluating the results of the study.

‖ Reference 32. Goodman and Gilman,[24] p. 546.

Each subject (control or patient) was studied on three occasions. Because the same time of day could not be utilized for each subject, the occasion on which a particular test was performed was deliberately varied. Thus, on the first occasion one-third of the subjects received Drug A; one-third received Drug B, and one-third received Drug C. Group I received Drug B on their second occasion;

Group II received Drug C; Group III received Drug A, etc. All subjects were allowed to lie at rest for 15 minutes,[33] during which time a warning and reassurance of the side-actions of the drug to be administered (i. e., palpitations, dyspnea, and anxiety following epinephrine; warmth, hypersalivation, lacrimation, and diaphoresis following methacholine) were given. Blood pressures were then determined every minute until five consecutive systolic and five consecutive diastolic readings did not differ by more than 5 mm. Hg. The mean of these five readings was used as a base line in the analysis of the results. On the first occasion 10 mg. of methacholine was given intramuscularly to one-third of the subjects, and pressures were taken every minute for 10 minutes, then every 2 minutes for an additional 16 minutes. In another third, 1 mg. of atropine sulfate was injected intramuscularly, followed in exactly 10 minutes by a similar intramuscular injection of 10 mg. of methacholine. Pressures were then taken every minute for 10 minutes and every 2 minutes for an additional 8 minutes.

The procedure was varied slightly on the occasion when epinephrine and phentolamine-epinephrine studies were done in that intravenous infusions of isotonic saline were started and allowed to run well before the 15-minute rest period began. After the pressure had stabilized, 0.05 mg. of synthetic *l*-epinephrine was injected into the distal end of the infusion-set tubing. Pressures were determined every 30 seconds for 5 minutes, and then every minute for an additional 5 minutes. After the pressure had stabilized for 10 minutes, during which time the infusions continued to run, 5 mg. of phentolamine, which was followed 2 minutes later by 0.05 mg. of synthetic *l*-epinephrine, was injected into the tubing. Pressures were determined as before. A fixed rate of infusion was maintained at the time of all injections.

All subjects were studied at least two hours after eating. A constant-temperature-humidity room was not available for the study. However, all testing was done in the same room, and the number of distracting influences was minimal. All subjects, including the schizophrenics, remained quiet during the study, although some of the latter were believed to be actively hallucinating at times. All injections were given by, and all blood pressure determinations were made by, the same observer, using the same anaeroid sphygmomanometer for all subjects, and rigidly following the current recommendations of the American Heart Association.[34] Although diastolic pressures were recorded and analyzed, the rapidly changing peripheral vascular bed following epinephrine made them extremely variable, and several diastolic readings were recorded with some doubt (as recommended by the American Heart Association ¶).

Observations on the degree of side-action and of the subject's emotional reaction were also made.

TABLE 2.—*Blood Pressure Responses to Epinephrine, Phentolamine-Epinephrine, Methacholine, and Atropine-Methacholine*

Test	Range of Response, Mm. Hg		Coef. of Variation*		Duration of Response (Means), Min.		Maximal Changes (Means), Mm. Hg		*P* of Latter Means, by *t*-Test
	Schiz.	Controls	Schiz.	Controls	Schiz.	Controls	Schiz.	Controls	
Epinephrine									
1. Systolic	73.4	24.4	369	15	4.5	3.1	+56.4	+57.2	Not signif.
2. Diastolic	65.2	100.8	1,121	96	...	...	−2.12	−35.65	$P=0.05$
Phentolamine-epinephrine									
3. Systolic	56.4	20.4	57	24	4.1	4.0	+25.8	+29.8	Not signif.
4. Diastolic	66.4	55.6	58	38	...	...	−42.8	−56.2	Not signif.
Difference 1-3	38.2	20.0	40	28	...	...	+30.56	+27.35	Not signif.
Methacholine									
5. Systolic	20.8	21.6	31	37	9.4	7.9	−21.8	−20.2	Not signif.
6. Diastolic	56.8	53.6	68	65	...	...	−29.4	−29.3	Not signif.
Atropine-methacholine									
7. Systolic	15.6	12.8	37	30	7.2	6.4	−11.5	−7.3	$P=0.05$
8. Diastolic	16.0	15.0	51	68	...	...	−8.9	−7.1	Not signif.
Difference 5-7	30.2	18.6	83	53	...	...	10.31	13.00	Not signif.

* Coefficient of Variation $\frac{\text{Standard Deviation} \times 100}{\text{Mean}}$

RESULTS

The schizophrenic and control groups were compared with regard to the intensity of the maximal systolic change, to the time it appeared, to the time it took the systolic pressure to return to normal, to the intensity

¶ Reference 34, p. 7.

of the diastolic change, and to the variability of all reactions. No differences were observed in the latencies of the reactions. Table 2 summarizes the other comparisons.

Thus, it will be seen that the variation within the schizophrenic group is, in almost all situations, appreciably greater than the variation within the control group. This finding, together with that of the longer time required for schizophrenic homeostatic mechanisms to work, has been noted by several others before.# It is also apparent that the differences in the intensity of the reactivity in the two groups is not marked. If the statistical accident (because of the tremendous variability) in the somewhat questionable diastolic responses to epinephrine is ignored, only the difference in the systolic responses to atropine-methacholine remains significant * (and barely at the 0.05% level). One other observation, which is in agreement with an earlier one by Freeman and Carmichael,[13] is the tendency of the schizophrenic diastolic pressure to fall after epinephrine, while the nonschizophrenic diastolic pressure tends to rise. However, with the exception of the variability and delayed homeostasis. The results of the present study would seem to join those of the minority of workers who found little difference in the reactivity of schizophrenic and nonschizophrenic end-organs.

There were no apparent differences in the intensity or duration of the side-effects of the drugs employed. As would be expected, the schizophrenics as a group reacted less emotionally (objectively and subjectively) than the control group.

No differences were elicited in the reactivity or degree of side-effect in the deteriorated and nondeteriorated schizophrenics, or in the various types of schizophrenic reaction, although the samples are admittedly too small to warrant any conclusions in this respect.

References 7, 13, 17, and 20.

* It is always possible that when a large number of tests are performed the results of any one may appear significant by chance itself.

II. BLOOD PRESSURE RESPONSES TO AUTONOMIC INHIBITORY AGENTS

Most of the authors who have been bold enough to formulate theories about autonomic abnormalities in schizophrenia seem to find evidence that the parasympathetic system is functioning to a greater degree than the sympathetic. These are reflected in the older, now known to be incorrect, concepts of "vagotonia," and in the recent, not yet shown to be incorrect, concepts of a "sluggish sympathetic reactivity,"[20] or "diminished central sympathetic reactivity."[35]

If the degree of sympathetic tone is diminished in schizophrenia, one would expect that the administration of minimal amounts of a sympatholytic agent (i. e., one which inhibits or abolishes the effect of tonic sympathetic discharge) to schizophrenics and nonschizophrenics would produce a greater change in the former than in the latter. (The nonschizophrenic group would have a greater degree of sympathetic discharge to be inhibited.) There are several such agents, and the one used in the present study is phentolamine. This is a new imidazoline derivative, which in intravenous doses of 5 mg. has been shown to possess mildly sympatholytic properties, as evidenced by its slight hypotensive action.[36] It also shows marked antagonism to the excitatory actions of circulating epinephrine, for which purpose it was employed in Part I. Unlike Dibenamine and other sympatholytic agents, it has no central vasomotor action.[38]

Administration of large doses of a parasympatholytic agent (e. g., atropine) might also lead to detection of differences among groups of differing autonomic activity. This, as reflected in blood pressure changes, might be possible, not as Hoffer[37] postulates, through the unopposed nicotinic action of circulating acetylcholine on sympathetic ganglia, but, rather, through differences in the increased cardiac rate (and thus cardiac output) which occur as a result of atropinization. That the slight blood pressure changes which follow atropine administration are reflections of the changes in cardiac output,

rather than in the peripheral vessels, appears to be well established.† Thus, with intramuscular doses of 3 mg., which all authors † agree will accelerate the heart rate, it would be extremely difficult to explain a fall of blood pressure following atropine on a pharmacological-physiological basis.‡

I have dealt in such detail with the circulatory actions of atropine because Hoffer [37] has recently published his observations on the administration of 3 mg. of atropine to 180 schizophrenics and 140 nonschizophrenics. If his conclusion, that 80% of the schizophrenics show a fall in systolic pressure while only 20% of the nonschizophrenics (excluding psychopaths and epileptics) do so, is valid, a remarkable diagnostic test would now be available.

To test the validity of Hoffer's claim, and also the degree of sympathetic tone in schizophrenia (by phentolamine), the present study was undertaken. Since the changes in pressure are small, the results of the intravenous administration of 1 cc. of isotonic saline are also reported.

Review of the Literature

Despite the fact that both atropine [39] and Dibenamine [40] have been reported on favorably as therapeutic agents, the literature of the use of the blocking drugs in schizophrenia is relatively scant. Only two reports indicating the results of the sympatholytic agents on schizophrenic blood pressure could be found. In the first case [40] nine catatonics showed a mean rise in systolic pressure following large doses of Dibenamine, while normals were reported to show no change. In addition, the mean pulse rate of the catatonic group rose significantly higher than did the mean of the control group. In the other, Freeman and Carmichael [61] apparently noted few differences in response to ergotamine between schizophrenics and nonschizophrenics.

The number of studies involving atropine is somewhat greater; however, as with most physiological studies in schizophrenia, few of the authors find agreement with each other. Several early workers,§ predominantly French, have reported atypical responses to Danielopolu's test of atropine and orthostatism,‖ but Ballif and Rosen [42] have shown that the results vary from month to month in the same person. Sachs [14] could find no characteristic response in 100 schizophrenics. Blood pressure responses differing from those of nonschizophrenics have been reported following injection of 6 mg. subcutaneously,[4] 3 mg. intramuscularly,[37] and an unstated amount.[7] No differences have been observed following 0.75 mg. intravenously [8] and 1.3 mg. subcutaneously.[28]

Materials and Methods

The drugs were administered to 13 schizophrenic patients who were part of the group described in Part I. Nine controls (of the group described in Part I) received atropine and saline; ten received phentolamine. The procedure followed was similar to that of Part I. On the first occasion, after the 15-minute rest period and 5 minutes of constant pressure, one-third of the subjects (both schizophrenics and controls) received 3 mg. of atropine sulfate intramuscularly. Pulse rate and pressures were then determined 1 minute after the injection and every 5 minutes for 45 minutes. Venipunctures were performed after the stabilization period on another third on their first occasion. With the needle remaining in the vein, and before any medication was given, the blood pressure was determined again. If there was any change from the base line, additional pressures were taken until the pre-venipuncture level had been reached, and 5 mg. of phentolamine methanesulfonate dissolved in 1 cc. of distilled water was then rapidly injected. Pressures were then determined every 30 seconds for 5 minutes, and every minute for an additional 4 minutes. One-third of the subjects on their first occasion received 1 cc. of sterile saline given similarly to the administration of the phentolamine. All subjects were warned that they would experience xerostomia, cycloplegia, tachycardia, and possibly dizziness following the

† Grollman,[32] p. 268. Goodman and Gilman,[24] p. 546. Drill, [38] p. 27/3.

‡ Larger, more toxic doses may lower blood pressure through direct central action (Goodman and Gilman,[24] p. 546).

§ Cited by Sachs.[14]

‖ Increasing amounts of atropine are given intravenously until the vagus appears totally paralyzed (as determined by the effects of posture on the pulse rate). The pulse rate before and after atropinization is supposed to indicate the degree of parasympathetic and sympathetic tone.[41]

atropine study. The limitations and precautions noted in Part I apply here, except that diastolic determinations were recorded with considerably more confidence.

Results

The schizophrenic and nonschizophrenic groups were compared with regard to the intensity of the maximum systolic and diastolic changes, their latencies and durations, the directions of the maximal changes (i. e., whether a rise or fall of pressures resulted), and the variance within the groups. The maximal pulse rate changes to atropine were also analyzed. No differences between the groups were observed in the latencies and durations of the reactions. The other results are summarized in Table 3.

of blood pressure in psychiatric patients pay little attention to diastolic readings. This is unfortunate, however, as they have been shown to be less subject to temporary fluctuations, such as are produced by psychogenic impulses, than are systolic readings.[43] Furthermore, that they reflect changes in peripheral resistance, such as would occur when sympathetic tone is inhibited, more closely than systolic pressures is an accepted principle.[44]

The observation, that all of the control group showed a fall in diastolic pressure following minimal sympatholytic doses of phentolamine, while nearly half of the schizophrenics did not, might, therefore, indicate differences between the sympathetic tone of

Table 3.—*Blood Pressure Responses to Saline, Phentolamine, and Atropine*

Test	Per Cent Showing Rise in Pressure		Coefficient of Variation		Maximal Changes (Means), Mm. Hg		P of Means (t-Test)
	Schiz.	Controls	Schiz.	Controls	Schiz.	Controls	
Saline							
Systolic	46	22	182	145	−0.45	−3.24	Not signif.
Diastolic	82	78	167	146	+4.10	+4.36	Not signif.
Regitine							
Systolic	38	40	318	248	−2.60	−1.90	Not signif.
Diastolic	42	0	333	55	−2.28	−7.58	P=0.1
Atropine							
Systolic	76	78	120	133	+7.38	+5.33	Not signif.
Diastolic	92	100	68	21	+13.25	+17.4	Not signif.
Pulse rate	100	100	34	25	+28.55	+29.91	Not signif.

Thus, increased variability of the schizophrenic response is again apparent. It is also apparent that Hoffer's results could not be duplicated in the small series used in this study. It should be pointed out that most of the schizophrenics used in Hoffer's study were acute. All of those in the present series were chronic. However, Hoffer applied his atropine test to 67 chronic schizophrenics and recorded a fall in systolic pressure in over 60%. As is evident in Table 3, only 24% of the chronic schizophrenics in the present study showed such a fall. I am unable to offer any explanation for the differences in results of the two studies except to call attention to the difficulties discussed above in explaining a fall in systolic pressure following 3 mg. of atropine sulfate.

The diastolic responses to phentolamine must now be commented upon. Most studies

schizophrenics and nonschizophrenics. That the difference between the means of the maximal diastolic changes tends toward significance ($P>0.1$) might also be taken as evidence of diminished sympathetic tone in schizophrenia. However, the number of subjects investigated in the present study is not large enough to warrant any definite conclusions. In addition, when the phentolamine test was repeated in several of the same subjects, slightly different diastolic responses were obtained. It is felt, therefore, that further investigation of the sympathetic nervous system in schizophrenia with phentolamine and other blocking agents is indicated. Differences from nonschizophrenics might further be elicited by keeping the subjects in the vertical position, producing maximal sympathetic tone,¶ during the test, or by

¶ Best and Taylor,[44] p. 215. Drill,[38] p. 28/3.

using frankly sympatholytic doses (0.5 to 1 mg/kg. of body weight) of phentolamine. Current studies along these lines are under way in a much larger series of patients and controls.

III. BLOOD PRESSURE RESPONSES TO A PHARMACOLOGICALLY INDUCED SYMPATHETIC DISCHARGE

There is still a third method through which utilization of the autonomic drugs allows investigation of the autonomic nervous system. To insure that the method employed is fully understood, a brief review of some basic pharmacological principles is indicated.

Not only does acetylcholine, the physiological mediator of the parasympathetic nervous system, act peripherally on end-organs (i. e., its muscarinic action), but it also has a stimulating action on both parasympathetic and sympathetic ganglia (i. e., its nicotinic action). Most of the synthetically prepared, commercially available, cholinergic drugs lack this latter nicotinic action. Thus, methacholine (Mecholyl), despite a statement in a recent psychiatric publication, has never been shown to possess any significant stimulatory action on sympathetic ganglia.[46] By inserting an amide group in the methacholine molecule, it has been possible to produce carbachol,# a drug which retains the nicotinic action of acetylcholine,* in doses as low as 150γ.[47] If the administration of carbachol is preceded by enough atropine (estimated as 2-3 mg. in humans [38]) to block its muscarinic action effectively, its nicotinic effects (which are not inhibited by 2 mg. of atropine †) produce a chemical sympathetic discharge. Thus, the criticism that the autonomic drugs do not act on the autonomic nervous system is obviated.

If, as many authors ‡ believe, the sympathetic nervous system is functioning to a lower degree in schizophrenics than in nonschizophrenics, pharmacological induction of a sympathetic discharge in both groups should provide a greater change in the former than in the latter. (The nonschizophrenic sympathetic system, already functioning at a higher level in the direction of the change, would be altered less.)

Materials and Methods

Ten schizophrenics and six normals from the schizophrenic and control groups described in Part I served as subjects. The procedure used was similar to that employed in Parts I and II. After the 15-minute rest period and 5 minutes of constant pressure, each subject received an intramuscular injection of 2 mg. of atropine sulfate. Pressures were taken 1, 5, and 10 minutes after the injection (in an attempt to ascertain the role of the atropine itself on the pressure). Immediately following the 10-minute reading, 0.25 mg. of carbachol was injected intramuscularly. Pressures were determined one minute following the injection and then every second minute for 30 minutes.

Table 4.—*Blood Pressure Responses to Atropine-Carbachol*

Test	Time for Maximal Change (Means), Min.		Maximal Changes (Means), Mm. Hg		*P* of Latter Means by *t*-Test
	Schiz.	Controls	Schiz.	Controls	
Atropine-carbachol					
Systolic	19.4	15.0	+6.06	+3.17	Not signif.
Diastolic	14.2	14.4	+12.92	+10.67	Not signif.

Results

The changes in systolic and diastolic pressures in the two groups were compared with respect to intensity and latency. Table 4 summarizes the results.

Thus, it will be seen that, with the exception of a slightly increased time for the systolic change to reach its maximum in the schizophrenic subjects, no significant differences were elicited between the groups. As would be expected with postulated dimin-

Supplied as Doryl by Merck & Co., Inc., Rahway, N. J.

* Goodman and Gilman,[24] p. 438.

† Goodman and Gilman,[24] p. 424.

‡ References 6, 8, 20, 26, 35, and 37.

ished sympathetic tone, the schizophrenic group reacted with a greater intensity in both diastolic and systolic changes than the nonschizophrenic group. However, the number of subjects in each group was too small to stand the test of significance. Repetition of the test, using larger, perhaps intravenous, doses of carbachol, in greater numbers of subjects, might possibly elicit the differences sought in the present initial study.

Since the pressures of only a few of the subjects had returned to their preinjection levels at the end of the 30-minute observation period, the durations of the responses were not analyzed. The reason for the prolonged action can be found in the relative inability of circulating cholinesterase to inactivate carbachol.§

COMMENT

Before the era of the current application of psychopharmacological, biochemical, and endocrinological methods of study to psychiatry, those interested in the somatic aspects of schizophrenia seemed, for the most part, to concern themselves with the study of autonomic functions. With the entrance of the new techniques into psychiatric research, investigations of autonomic function seem to be less prominent. However, the autonomic nervous system is not being totally neglected by the new disciplines; on the contrary, there is hardly a phase of current physiological psychiatric investigation that does not in one way or another involve the autonomic nervous system. Thus, the action of chlorpromazine on the mediators of the sympathetic division has recently been emphasized,‖ and explanations of the effects of Rauwolfia derivatives in terms of sympathetic reactivity [48] and other autonomic functioning [49] have been offered. Autonomic changes have been reported in mescaline-[50] and lysergic acid-diethylamide-induced experimental psychosis.[51] The blood pressure responses to administration of epinephrine and methacholine have been reported to change in subjects receiving the latter drug.[52] Metabolic products of the sympathetic mediator have been suggested as having prominent roles in the pathogenesis of schizophrenia.¶ It could be postulated that the explanation for the recently reported differences in the pituitary-adrenal [54] and pituitary-thyroid [55] axes in schizophenics and nonschizophrenics might be found in the hypothalamus, a hypothesis which would correlate well with Gellhorn's [35] theory for the autonomic disturbances in schizophrenics.

The autonomic nervous system has often been pharmacologically investigated in connection with the various somatic therapies. Thus, Funkenstein and associates # find that the responses to methacholine and epinephrine change in all subjects who show improvement, regardless of the type of therapy. Furthermore, the change is in the direction of an increased reactivity to epinephrine.[57] The reactivity pattern has been claimed to be more reliable than the clinical impression for predicting prognosis.[45] The reactivity of the schizophrenic end-organs following insulin shock has been found to increase in response to both epinephrine [18] and methacholine.* There are several claims † of altered autonomic reactivity following various psychosurgical procedures.

One can only conclude from these and other studies that the investigation of the autonomic nervous system in schizophrenia is far from complete. Unfortunately, however, the number of accepted methods for adequately evaluating autonomic function are minimal. Despite the fact that many erroneous conclusions (i. e., those involving the concepts of vagotonia and sympathicotonia) were drawn from its early use, the method of pharmacodynamic investigation of the autonomic nervous system remains, it is argued in this paper, as valid. Through such techniques as utilization of the newer

§ Goodman and Gilman,[24] p. 438.

‖ Papers read at the Research Conference on Psychopharmacology, March 26, 1955, at McGill University, by H. E. Lehmann, A. Rothballer, and K. I. Melville.

¶ References 52 and 53.

References 17, 30, and 56.

* References 18 and 58.

† Referenees 19, 59, and 60.

adrenergic blocking agents, pharmacological induction of a sympathetic discharge, and others (e. g., employment of ganglionic-blocking agents, etc.), it should be possible to answer some of the many unanswered questions about autonomic function in schizophrenia. It is hoped that the present study has served as a guide for future attempts to find the answers.

SUMMARY AND CONCLUSIONS

In an attempt to elicit differences between the functioning of the autonomic nervous systems in schizophrenics and in nonschizophrenics, small, carefully selected samples from each group were subjected to several pharmacodynamic investigations. Both a sympathomimetic agent (synthetic *l*-epinephrine) and a parasympathomimetic one (methacholine [Mecholyl]) were employed alone, and together with their respective blocking agents (phentolamine [Regitine] and atropine). The sympatholytic (phentolamine) and parasympatholytic (atropine) agents were then employed independently. Advantage was also taken of the nicotinic action of carbachol in atropinized subjects to produce pharmacologically induced sympathetic discharges.

The rationale for using pharmacological agents to study autonomic physiology is stated; the literature on the use of autonomic drugs in schizophrenics is reviewed, and an attempt is made to explain some of the reported conflicting results of previous investigators.

The results of the present study are not striking. The diminished reactivity of schizophrenics to injected epinephrine described by a majority of authors and the results of Hoffer's atropine test could not be confirmed. A definite tendency toward differences between the responses of diastolic pressure of the schizophrenic and the nonschizophrenic groups to phentolamine was elicited, and a possible tendency toward differences between the groups as a result of the pharmacologically induced sympathetic discharge was noted. As several previous studies have shown, the schizophrenic reaction is characterized by greater variability and slower homeostatic mechanisms than is that of the control group.

The literature indicating the importance of the autonomic nervous system (with emphasis on its pharmacodynamic aspects) in many of the current biological-psychiatric studies of schizophrenia is reviewed. The usefulness of pharmacological methods of study is restated, and plans for further investigation are presented.

Rockland State Hospital.

Drs, Per Vestergaard and John H. Blair and Mr. Ashton M. Tenney gave aid and encouragement in this study; Miss Nancy Buckley, Mrs. Amparo Chamberlain, R.N., and others of the Rockland Research Facility assisted, and Dr. Otto Loewi, Research Professor of Pharmacology at the New York University College of Medicine, criticized the manuscript.

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The Syndrome of Apractognosia Due to Lesions of the Minor Cerebral Hemisphere

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1. Introduction
2. Case Material
3. Survey of Literature (H. H.)
4. Case Analysis (H. H.)
5. Auras and Sensations (H. H.)
6. Note on Localization (W. P.)
7. General Comment
8. Summary

Perhaps the setting of this study, which extends over a 10-year period, should be described at the outset. The patients reported were admitted, at various times, to the neurosurgical service of one of us (W. P.) in the Montreal Neurological Institute. The earlier cases were studied there by C. B. (now of Hôpital Notre Dame, Montreal). In 1952 H. H. (Hôpital Ste. Anne, Paris) spent a six-month period in Montreal, and many of these patients were called back so that he might study them carefully in the light of his previous interest in parietal lobe function. The remaining author, R. M. (Department of Psychiatry of McGill University), undertook special psychological studies of these patients.

The argument, in Sections 3, 4, and 5, was originally written by H. H. and is presented, with minor changes, after general discussion. A note on localization is added by W. P. in Section 6.

1. INTRODUCTION

The syndrome of apractognosia due to lesions of the minor (nondominant) cerebral hemisphere is a subject of ever-increasing clinical interest. What is the difference between the defects produced by lesions of the minor parietal cortex and the defects resulting from lesions of the parietal cortex on the dominant side? What can the functional defects that constitute this syndrome teach us in regard to the uses of the right parietotemporal cortex under normal conditions? Does a study of the results of electrical stimulation, and of the epileptic auras which may arise from discharge in the area, contribute anything to an understanding of these problems?

With such questions in mind, we studied a series of patients who had practognostic disturbances after well-localized parietal or parietotemporo-occipital excisions. These excisions had been undertaken for the cure of focal epileptic seizures. They were made after careful identification of the convolutions to be removed and those to be left unharmed. Each removal involved the cortex alone. The circulation of surrounding cortex, as well as of subcortical areas, was carefully preserved.

During clinical examinations we have searched for defects in regard to the following: praxis (apraxia for dressing; ideational, ideomotor, and constructive apraxia); body scheme (awareness of the body-half, right and left orientation, finger gnosis, and autotopagnosis); spatial gnosis (spatial orientation, topographical relationships, notion of distances, notion of depth, map orientation); visual gnosis for images and objects with tachystoscopic examinations, perception of visual coordinates (subjective horizontal and vertical); calculation and counting, time and rhythm appreciation; oculomotor movements, with graphic recordings. In some

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cases we have been able to refer to psychological examinations.

We have made a detailed study of 17 patients of this type and have reexamined 13 of them after considerable periods of time. Four other cases, examined previously both from the clinical and from the psychological point of view, were also included, since the presence or absence of apractognosia had been carefully recorded.

Of the 17 cases, 15 have to do with excisions in the right hemisphere in right-handed persons and 2 with removals on the left side in left-handed persons. In other words, our investigation deals with the minor parietal or parietotemporo-occipital syndrome.*

Of the 17 patients, the apractognosic syndrome was found in 10, but the report of one of them was set aside because of his low intelligence rating, reducing the total cases to 16. Of the nine positive cases (apractognosic syndrome), we shall describe only the five most representative, together with a summary of the control case (Case 6).

Although an analysis of the sensory defects is not reported here, it should be mentioned that in this group no change in cortical sensation has resulted from any parietal excision which did not involve the postcentral gyrus.†

2. CASE MATERIAL

In these cases it is possible to state with certainty which convolutions were removed at operation. Repeated electroencephalographic studies and follow-up examinations provide further useful information. Thus, the detailed description of postoperative examinations as compared with studies carried out before operation should, we believe, add valid evidence for the study of functional localization in the parietal region of the minor hemisphere.

It is necessary to bear in mind that before operation in each case there had been cortical injury followed by local epileptic discharges. When the injury was gross and when it occurred early in life, there may well have been some displacement of functional representation. It should be borne in mind, also, that the epileptic state which involves a localized area of cortex may also interfere with local cortical function as long as it continues.

These removals were carried out in the minor hemisphere, that is to say, the hemisphere in which speech did not have its dominant representation. The hemisphere was also nondominant as to handedness in most, and perhaps in all, cases.

CASE 1.—*Brain injury at age 4; seizures from age 16; excision of right parietal cortex, exclusive of postcentral gyrus, at age 25; resulting marked apractognosia, disappearing gradually over a 15-month period; postoperative freedom from seizures.*

The patient, a right-handed man, age 25, was admitted, to the Montreal Neurological Institute for treatment of focal seizures on Jan. 16, 1946.

He had sustained a depressed right parietal fracture at the age of 4 years, for which operation had been performed immediately. Some fragments of bone had been removed. He seemed to progress normally afterward. Seizures appeared at the age of 16 and recurred approximately every six weeks thereafter.

His attacks were described as follows: "He has a vague warning; he cannot see very well; he does not know just where he is; he has trouble in speaking because he cannot concentrate; it is hard for him to understand what others are talking about. He then turns to the left and may describe a half-circle before he falls, becomes unconscious, and bites his tongue in a major convulsive seizure. Frequently, he suffers from 'foggy' attacks, with blurred vision and, possibly, diplopia."

* However, we have considered one observation in regard to a cortical excision in the left posterior parietal region in a right-handed person. (He had remained aphasic for more than a year after his injury. His seizures were preceded by an aura of aphasia. There was a transitory nominal aphasia postoperatively.) When he was examined again in October, 1952, six years after his operation, there was no evidence of spatial agnosia, no constructive apraxia, and no asomatognosia. On the other hand, there existed a definite discrepancy between his performance I. Q. (102) and his verbal I. Q. (86). As we shall see, the opposite result was evident in the psychological examinations of patients with a symmetrical removal in the minor hemisphere.

† It is difficult at this time to explain the case published by Evans (1934) in which such a lesion produced sensory change. There may have been an unsuspected subcortical lesion.

A brief summary of the literature will be presented, following the case reports, so as to draw a composite picture of the syndrome produced by lesions of the posterior portion of the minor hemisphere.

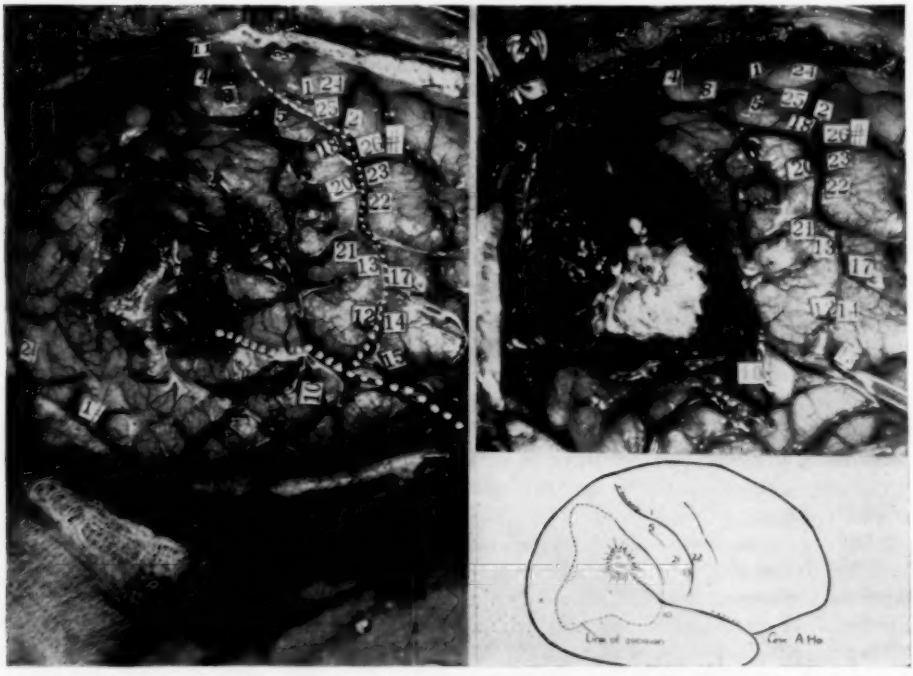

Fig. 1 (Case 1).—Photographs of the brain at operation. In the left panel, the dotted white line has been drawn in the central fissure, above, and the fissure of Sylvius, below. The scar in the supramarginal area is obvious. The points of positive response to stimulation are marked by numbered tickets. In the right panel and in the inset, the extent of cortical excision is indicated exactly. The white matter is exposed, and the pial covering of the remaining convolutions is preserved. This patient has had no attacks in the nine years since operation.

Stimulation responses were as follows: Precentral gyrus: *1*, movement of left arm at shoulder; *2*, movement of left arm at elbow; *26*, turning of both eyes to left and closure of lids; *17*, opening of mouth; *15*, swallowing. Postcentral gyrus: *11*, left shoulder "wanted to move"; *5*, sensation that middle finger (left) was being pushed in; *13*, sensation on left side of mouth. First temporal convolution (auditory): *10*, "sound like a motor, low-pitched" (repeated twice, the same). Posterior temporal cortex: *1♯*: "Just a minute! Like a figure on the left side. Seems like a woman. I think it was a woman. She seemed to have nothing on." *1♯* (repeated): "Same damn thing!" *2♯*: "I wish I could describe this. Steps with people trying to rise up." *2♯* (repeated): "This is the funny feeling I get. I thought I saw a person. I think it was a man." He explained he had had the feeling that habitually preceded an attack.

Neurological examination was negative upon admission, and he was found to be of average intelligence. There was a right parietal bone defect, 5 cm. in diameter. A pneumogram showed the ventricles to be moderately enlarged on both sides, but this was most marked in the posterior portion of the right lateral ventricle under the bone defect. The electroencephalogram suggested a right cortical epileptogenic lesion in the central and parietal regions. The test showed "spike" and "sharp-wave" activity in the region of the cranial defect.

Operation.—A right osteoplastic craniotomy exposed the posterior half of the right hemisphere. Beneath the bone defect a meningocerebral scar was found, and beneath that a cyst within the brain. Careful study was made of the exposed cortex by stimulation and electrocorticography. The brain lesion centered in the vicinity of the supramarginal gyrus (Fig. 1, left panel). The gray cortex was removed about the lesion and down to white matter. The removal was extended out to fissure lines by use of a sucker. Thus, cortex was removed from just posterior to the postcentral gyrus backward and downward into the first temporal convolution and a little way into the occipital region (Fig. 1, right panel). This was a large removal of parietal and posterior temporal cortex, excluding the postcentral gyrus, which was carefully preserved (drawing, Fig. 1).

Postoperative Course.—A postoperative electroencephalogram carried out 16 days later was reported by Dr. H. Jasper as follows: "The cortex

which was producing epileptiform discharges seems to have been removed successfully, but the amount of slow waves and of 6-per-second dysrhythmia is increased."

For a few days following operation the patient had complete loss of two-point discrimination, position sense, and point localization in the left hand and impairment of position sense and two-point discrimination in the left foot. Fourteen days after operation there remained very little defect in the sensory examination. The patient was subjected to detailed neurological and psychological examination before leaving the hospital, and later he returned to Montreal for postoperative examinations.

Before the details of more careful examinations are presented, the surgeon's follow-up notes, (*a*), (*b*), and (*c*), may be quoted:

(*a*) Three and one-half months after operation one of us, W. P., made the following note: "On first returning home, the patient was practically unable to dress himself. He might put his pajama coat on his legs, or he might try, up to 10 times, to get his lower pajamas on properly and fail. At such times he would be apt to break into uncontrolled fits of temper. . . . One evening he came home late, and members of his family had gone to bed; he could not get his cuff links off, so he tore his shirt to pieces.

"His mother says that he moves around too fast and is apt to spill things over. His parents noted also that at the dinner table he would keep his left hand in his pocket, and have a good deal of difficulty in feeding himself with the right until they reminded him about using his left hand, whereupon he would take it out and get along quite well. He seemed to have forgotten his left hand.

"On going back to work in his father's clothing store, about three months after his operation, he found that what used to be easy was hard to do. He realizes that he dresses mannequins in the store more easily than himself, and he suggests this is due to the lack of movement in the mannequin and necessity for moving parts of his own body when dressing himself. He seemed at first to have forgotten most of the things about the store. He found it particularly difficult to work out problems in bookkeeping, and on one occasion he had to stop and walk out of the store. He has no difficulty in reading.

"On physical examination, the deep reflexes in his left [contralateral] arm seem to be normally active, but those in the right are less so, being a little hard to elicit, except with reinforcement. Deep reflexes in the lower extremities are equal. Abdominal reflexes are absent on both sides. Two-point sense in the left hand is equally as good as in the right."

(*b*) Eight and one-half months after operation the surgeon made the following note:

"He has had no attacks and has been feeling well. Physical examination: Letter and number writing on the skin was detected with equal accuracy on the two sides. He still had some difficulty in memory. When told to carry out a series of movements with either hand, such as touching my thumb, his right ear, then my nose, he seemed to become confused and made some errors, but he always performed the correct number of maneuvers. His mistakes were as frequent with one hand as with the other. When I asked him to go and pick up a flashlight, then to turn off the light, he carried out the task perfectly.

"Two-point sense is obviously completely normal. In mental arithmetic he is as quick as, or quicker (!) than, I am. He explains to me that his difficulty in keeping books is in transferring items from one book to another and in remembering which book he should transfer to. In a sense, this seemed to be an inability to visualize. I should think, also, that his difficulty in carrying out the little hand problems given him above was due to a similar difficulty in visualizing the act as fast as it was described to him."

(*c*) Fifteen months after operation the surgeon's follow-up note was as follows:

"There is no abnormality whatever in the pointing test. He says he occasionally knocks things over because he has a little loss of vision in the left visual field. Otherwise, he can notice nothing wrong with his hand, himself. Rather complicated pointing tests are now carried out equally well on the two sides. He has little or no trouble, now, with 'double-entry bookkeeping.' He thinks that his memory is not perfect, but, as far as he can remember, it was 'just as bad, or worse, before operation.'"

Examinations (C. B. and R. M.).—There was a partial left homonymous hemianopsia, the defect occupying the greater portion of the left lower quadrant: Objects seen in the upper quadrant of the left visual field were well identified, even when small, but the patient occasionally stated they were "not as clear" as on the right side.

Motor power and tendon reflexes were found to be normal. Muscle tone on the left was somewhat reduced during the first postoperative weeks but became normal. Coordination of movements was good in either hand when both hands were used simultaneously during the two-hand coordination test.

No specific sensory impairment could be detected on the left side. The only abnormality in the sensory field was found in the localization of tactile stimulation to the various fingers. This was restudied with a great number of stimulations on Oct. 2, 1946, more than eight months after opera-

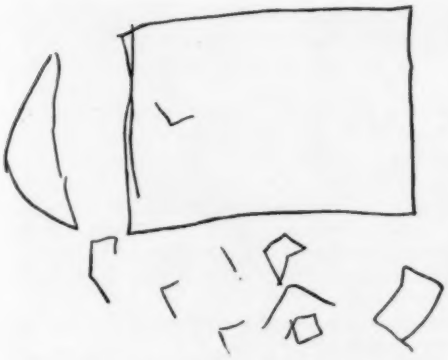

Fig. 2 (Case 1).—Attempts to draw the outlines of differently shaped blocks from "tactual memory." The large rectangle represents the outline of a form board (Halstead Tactual-Performance Test) with which the patient had worked while blindfolded. When the test was finished, the subject's blindfold was removed, and he was asked to draw the board and the blocks which he had been trying to place in the various holes. Within the rectangle is patient's initial attempt to draw a star-shaped block. Below the rectangle are further attempts to draw a star. On the left is a half-circle, which is a correct representation of one of the blocks.

tion. The frequency of error in naming the finger touched was then found not to be significantly greater in the contralateral hand than in the ipsilateral (14/150, or 9.3% error, for the left hand and 11/150, or 7.3% error, for the right hand). Factors of stimulus intensity and fatigue did not appear to be important. Moreover, 22 of the 25 errors which the patient made consisted in misnaming the ring finger when it was touched.

The visuoconstructive deficiencies of this patient, during the early weeks after operation, were evident when he was asked to draw, from memory, the Halstead Form Board which he had just handled (blindfolded), and to draw in the blocks in their correct positions on the board. He thought that the board was a perfect square. In reality, it is considerably taller than it is wide. He then attempted to draw in the star, and he seemed surprised that he could not make one. Figure 2 shows his various futile attempts to draw the star. He could not draw a cross (Fig. 3).

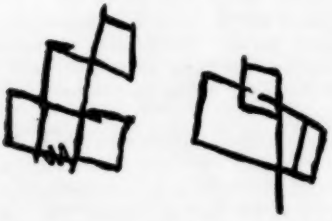

Fig. 3 (Case 1).—Patient's attempts to draw a cross 21 days after operation.

Three and one-half months after operation the patient could draw a cross but still could not draw a star. After eight and one-half months the patient could draw a six-pointed star, which he had practiced at home, but he was at a loss when asked to draw a five-pointed star. The patient was accurate in copying stars and swastikas, which he could not draw from memory.

This patient experienced difficulty generally in drawing. His drawing of a man (Fig. 4) is an example of this. The score on the Goodenough Draw-a-Man Test was 21, which corresponds to a "mental age" of 7.3.

His performance on "mutilated words" and "incomplete pictures" (Street Gestalt Completion Test used by Thurstone) and his ability to find "hidden figures" (e. g., Gottschaldt figures arranged by Thurstone) makes it appear that he could fill in gaps visually and could organize perceptual configurations in the presence of lines which were purposely added to make such configurations hard to see. However, in this test, it is perhaps significant that the subject failed an item which required working with three dimensions (Fig. 5).

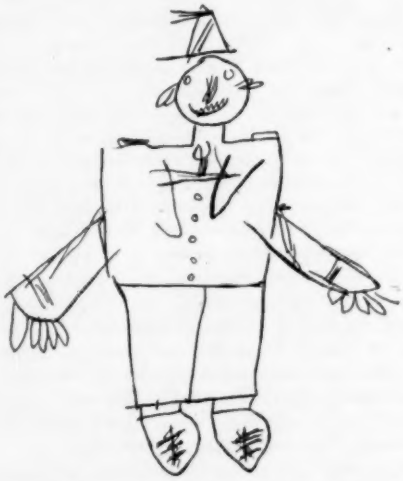

Fig. 4 (Case 1).—Drawing of a man made three and one-half months after operation.

There is another observation of interest. With eyes closed, while trying to think of what his left hand looked like, the patient said that his left hand seemed to be moving toward the right side of his body. This sensation of movement to the right he also noted when trying to visualize his right hand. He said that it was as though he were trying to get it over to the center so that he could

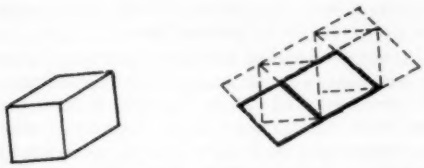

Fig. 5 (Case 1).—Performance on "hidden figures" test. On the right, the heavy black lines show the patient's attempt to trace the model placed on the left. The reader can see how, by tracing other dotted lines, it is possible to reproduce the three-dimensional figure.

see it more clearly but was unable to do so because it would not move that way.

No spatial disorientation was found: Distances were well appreciated; lines were correctly bisected in the middle.

Agreement was close between scores on the Wechsler-Bellevue Intelligence Scales obtained three and one-half and eight and one-half months following operation. In order to reduce practice effects, Form I was administered on the first testing and Form II on the second. In both instances there was marked discrepancy between the verbal I. Q. and the performance I. Q. On the first test verbal I. Q. was 113; performance I. Q., 73. On the second testing, the corresponding values were 112 and 73. This finding provided further evidence that perceptual motor abilities were far more affected than verbal abilities. The two administrations of the Stanford-Binet vocabulary test placed the patient among superior adults.

CASE 2.—*Brain lesion at birth; seizures from 10 years of age; operation at 17 and 18 years, in two stages, right lower central and right parietal cortical excision; seizures not arrested.*

This right-handed (but left-footed) youth of 17 suffered from focal seizures. He had had paralysis of the left arm and the left side of the face for a few days after birth, but on admission the neurological examination was negative. Seizures began at the age of 10 years. They were left-sided but were ushered in by an aura of fear. It was concluded that he had a diffuse atrophic lesion of the right hemisphere, and he was operated upon twice in the hope of stopping his seizures.

The first operation was carried out on Feb. 18, 1949: right craniotomy with excision of the inferior portion of the pre- and postcentral gyri, frontal operculum, and a part of the adjacent temporal lobe (dotted line *A*, Fig. 6).

In the subsequent 16 months he had done well in school but had had four major seizures, ushered in by a bodily aura. Electroencephalography showed active discharge in the postcentral area. Consequently, a second operation was carried out, on June 29, 1950. Some microgyri were discovered in a depressed region behind the postcentral gyrus His aura was reproduced from the postcentral gyrus, but electrical discharges were most marked posterior to that region.

Still with the hope of decreasing the tendency to attacks, further excision was carried out in the parietal lobe, including a small portion of the postcentral gyrus. The extent of excisions in the two operations is shown in Figure 6.

Neurological examination carried out two weeks later, on July 15, disclosed slight left hemiparesis with increased deep reflexes on the left. There were slight hypertonia of the left arm and slight left facial paresis.

Appreciation of passive movement and perception of light touch were diminished all over his left side, including the face. There was an extinction phenomenon on that side in a bilateral painful stimulation. There was a "relative" left hemianopsia for small objects.

Results of the intelligence tests have been tabulated:

Verbal Tests	June 27, 1950 (Before Second Operation)	July 14, 1950 (After Second Operation)
Stanford-Binet Vocabulary	27	26 (average adult)
Wechsler		
Information	15	15 (superior adult)
Similarities	12	11 (superior adult)
Analogies (McGill)	27	26 (superior adult)
Wechsler "Digit Span"	12	12 (superior adult)
Picture Anomaly series (McGill)	27	21 (30 on July 19, 1950)

It is evident that his verbal I. Q. was definitely superior to the average adult's and that it was not modified by his operation; there was a transitory disturbance in perception of inappropriate details in complex pictures.

Fig. 6 (Case 2).—Excision of cortex at the first operation, shown by broken line (*A*). Excision at the second operation, 16 months later, shown by line *B*. This second excision was entirely posterior to the postcentral gyrus, except for a narrow atrophic area at the junction of sensory leg and sensory arm areas.

Psychological examinations carried out by our associate, Dr. Brenda Milner, two weeks after the second operation, are of considerable interest.§

Spatial Tests.—His score was slightly below average in the test with Wechsler cubes (based on the Kohs test) even before his second operation (corrected score of 8). He built every model; only he did so too slowly. After his operation his level deteriorated considerably, to a score of 4. He wanted to blame his failures on his paretic left arm, even though he could finish only the most elementary outlines taking as much time as he wanted to.

Also, he experienced great difficulty in filling a triangular and a rectangular hole with four identical triangles. While he had succeeded in 50 seconds before operation, it took him 2 minutes and 30 seconds after his operation. He also neglected the lower left side of the sheet in the written tests given him during the postoperative period.

Third Admission, June, 1952 (recalled for study by H. H.).—The attacks had persisted. They were about as frequent as before and there was sometimes loss of consciousness. His mental ability had diminished gradually, although he had graduated from school a month before (his mother stated that his professors had certainly been indulgent toward him). There seemed to be more difficulty in walking.‖

Electroencephalography revealed a generalized dysrhythmia with a localized discharging area near the right central region.

On neurological examination no muscular weakness was found. The left upper limb could definitely be hyperextended, and there was a slight incoordination in the finger-to-nose test of that limb.

Sensory examination revealed only some impairment of touch localization and of position sense (in passive movements of the left fingers). On the left side of the face two-point discrimination was slightly deficient. Position sense was impaired bilaterally in the toes; two-point discrimination was inadequate over the left foot. The extinction phenomenon was present over the entire left side during bilateral simultaneous stimulation.

Examinations Between June 11 and 13, 1952.—Speech: There was no difficulty in understanding or in articulating words. His vocabulary was intact. Reading was well performed. Writing from a copy or from dictation was without fault except for orientation of the written lines.

Arithmetic: Mental arithmetic was good when he was adding or multiplying, but he made mistakes in subtracting: 83—17=76; 38—11=79. He read and wrote figures well, but he made errors even in simple operations: The figures were placed correctly and the principle of the operation was followed, but he used figures inaccurately. He and his mother mentioned that his greatest difficulty in high school concerned mathematics.

He could number well objects placed in line or scattered about. While he was doing this, his head moved continuously.

No difficulty in ideational, ideomotor, or melokinetic praxis.

Dressing Apraxia: He was unable to tie his necktie, having great difficulty, at the outset, in putting the larger side of the tie where he wanted it; because of this he took it off many times, but the result was always the same. He then tried to put the narrower end over the other, but he could not even start the knot and he gave it up. In front of us, he put on and took off his vest and his pants without difficulty, but his mother stated that sometimes she must help him, and that was especially true shortly after his operation. He had great difficulty in tying his shoe laces and sometimes must also be helped with that. He mentioned spontaneously that he frequently confuses his right and his left shoe when he puts them on.

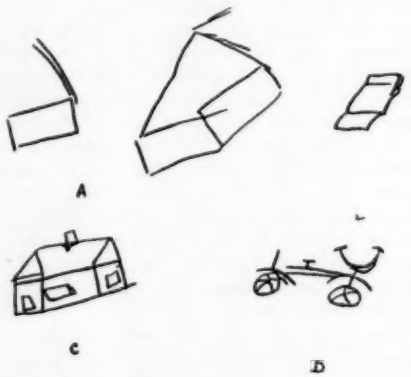

Fig. 7 (Case 2).—Tests carried out two years after the second operation. *A*, attempts to copy a cube; *B*, drawing of cube without model; *C*, drawing of house from a model; *D*, drawing of bicycle without model.

Visuoconstructive Praxis: Drawing on command of flat and geometrical figures was well done (square, triangle, circle). His star was not so good, although he seemed to figure it out well in

§ The defects which she found in regard to spatial relationships were still present two years later, in 1952.

‖ It may well be that if the seizures had been arrested in this case and if he had been taking less medication he would have made better scores at this time. This factor must be borne in mind in this case.

theory. He failed as soon as he was asked to draw a cylinder, a cube, and, to a slighter degree, a pyramid; for example, the different parts of the cube were laid down, and he could not produce the illusion of volume (Fig. 7*B*). The presence of a model helped a little, but the result was still poor because he could not imagine the different planes involved (Fig. 7*A*). The same obtained for the cube, the cylinder, and the pyramid. On the other hand, his copy of a house with perspective is better (Fig. 7*C*). Yet it does not give the impression of perspective. The drawing of a bicycle (Fig. 7*D*) on command is especially childish, and the relation of the various elements is inadequate. The frame is drawn with a single line, and the seat is placed on the middle of it. With a model, he only approaches the appearance of a bicycle, and relationship of the parts is no better.

It was when he was asked to draw a man that the result was most disorganized. Although he

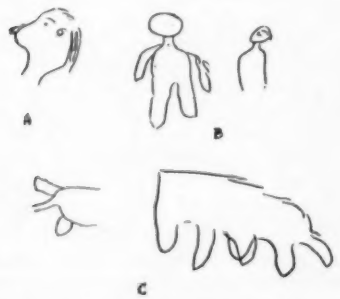

Fig. 8 (Case 2).—Tests two years after second operation. *A*, drawing, to command, of a face in profile; *B*, attempts to draw the mannikin; *C*, attempts to draw a hand.

tried many times, the final result was very poor. The lower limbs were in direct continuity with the body, a straight interior line breaking the general oval shape; he had great trouble in fixing the upper limbs to the body. His profile of a face was just as primitive; so was his drawing of a hand; in the first attempt, having drawn a curved line, he tried to add the fingers; they were represented by three ovals, one of which was not even closed. He numbered the fingers and gave up, seeing there were only three fingers. He started again, tracing one finger after another and counting, but the result was extremely abnormal (Fig. 8*A, B, C*).

Wertheimer-Bender Test: Although the tracing was clumsy, most of the figures were reproduced accurately. Items 2, 3, and 5 of this test, which are made of lines formed by dots, were the best. In the case of Item 2, the oblique orientation of the circles was lost, and in Item 3 he was unable to give the general shape because he did not draw in a parallel fashion. Finally, although trying intently, he could not reproduce the rounded appearance of the main part of Item 5 of the test.

Building with sticks, either spontaneously (square, triangle) or from a model (house, cube), was well accomplished, but it was done in following the contours one after the other. Construction of a rectangle from different parts falling one into the other was done quite rapidly.

Somatognosis: It was difficult for him to identify the right and left of the examiner placed in front of him. When asked to take the examiner's left hand, he took the one which was in front of his own left hand. When the examiner turned around while he was holding his left hand, he was "lost" when asked where the examiner's left hand was. This right-left trouble applied to the external world (for example, he mixed his shoes). At first, he was also confused when shown similar drawings but with the base of one of them inverted; after a few mistakes he succeeded in recognizing them as similar. He was unable to transpose and copy the movements of the examiner in the hand-eye-ear test of Head.

Finger Gnosis: It was very difficult for him to name his own fingers on command; he frequently mixed the index and medius. He seemed unable to number his fingers in any constant fashion in a given direction. When the examiner's hand was placed beside his own and he was told to copy movements, such as touching with the index of his other hand the same finger the examiner had touched, he did it accurately. However, if the examiner's hand was placed beside his in the opposite direction, he made frequent mistakes for the three central fingers. When his eyes were closed, he was often inaccurate in naming the finger touched either on his right or on his left hand. There was no evidence of autotopagnosia.

Visual Gnosis: Colors, objects, and images were well recognized, even when they were quite complicated.

Spatial Gnosis: He was well oriented in the ward and in the hospital. He appreciated relief and distances. Nevertheless, his mother said that it was hard for him to go down, and even more to go up, stairs because "he does not judge distances," and he agreed with this. Likewise, when he wanted to sit on a chair, he sometimes misjudged his distance and sat beside it. Upon command he was able to reach, with his hand or foot, objects placed at different distances from him. He placed a cross accurately in the middle of a line. He reproduced fairly well the outline of the room in which he was being examined, although he changed the position of the bed, putting it on the left, instead of the right, side. The outline of his house was drawn correctly, as was his schematic map of the United States, with accurate placement of the main cities.

No unilateral spatial agnosia was noted. He appreciated the passing of time accurately. He was able to reproduce different rhythms.

Visual Coordinates: There is a two-degree deviation for the vertical and the horizontal line in a counterclockwise direction. This same deviation obtained for writing. He was unable to keep a straight line, although his attention was frequently drawn to that fact. He also placed his figures diagonally in arithmetical tasks.

Ocular Movements: The movements of the eyes seemed normal when he followed a pendulum or when he was reading. Optokinetic nystagmus was preserved when the object turned from his right to his left, but it was lost in the opposite direction.

Psychological Note (R. M.; June, 1952).—"In reviewing this patient's test findings, it must be recalled that he is still subject to occasional seizures and is taking anticonvulsive medication (conditions which might produce a general slowing). In making comparisons with the most recent testing of the previous patient (Case 1), therefore, it should be borne in mind that the patient had been free of attacks for six years following the operation, and up to the time of examination. Yet there appears to be a fundamental resemblance in the two cases, in both of which there was a marked discrepancy between the verbal I. Q. and the performance I. Q. In Case 2, the two values were 107 and 78, respectively.

Case 3.—*Intracerebral hemorrhage at birth or in infancy; seizures from 4 years of age; at 19 years excision of entire right parietal cortex, leaving postcentral gyrus for leg and arm (above hand) intact; relief of seizures except for sensations in arm.*

A right-handed youth of 19 was admitted to the Montreal Neurological Institute on April 23, 1947, complaining of frequent seizures, which had appeared first when he was 4 years of age. There were three kinds of attacks: (*a*) dizziness with vision of colored lights; (*b*) generalized seizures without any aura; (*c*) generalized seizures beginning with a tonic movement of the left arm. Neurological examination revealed left facial paresis, left hyperreflexia, and a deficit in stereognosis and two-point discrimination in the left upper limb.

His EEG favored a large lesion involving the right temporoparietal region. His pneumoencephalogram evidenced a ventricular dilatation, more marked in portion 4 of the right lateral ventricle. X-rays also revealed tuberculous lesions of the right lung.

The patient's situation was a desperate one, and it seemed advisable to stop or decrease his uncontrollable seizures before proceeding with treatment of his pulmonary condition. Operation was, of course, carried out with local anesthesia, as in all such cases.

Right craniotomy was performed on May 28, 1947. A lesion was found that must have been produced by an early cerebral hemorrhage (brownish-green tissue with an underlying cyst) in the parietal cortex posterior to the central fissure. Abnormal electrical discharges were most marked behind the cerebral cicatrix. The cortex and lesion were excised completely behind the fissure of Rolando and above the fissure of Sylvius. The postcentral leg area and the arm area (above the hand region) were left untouched (Fig. 9).

After operation treatment for his pulmonary tuberculosis was continued (pneumothorax, streptomycin). His postoperative EEG showed definite improvement. He had minor seizures involving the left arm only ("neighborhood attacks") at rare intervals. Major seizures disappeared.

The patient returned for a follow-up study Aug. 8, 1952, more than five years after operation. He

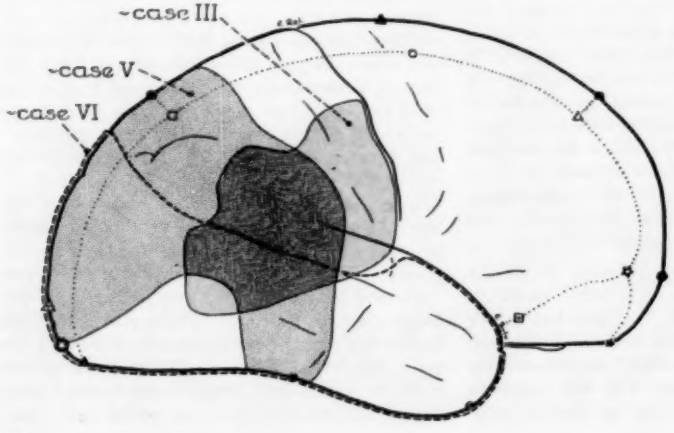

Fig. 9 (Cases 3, 5, and 6).—The extent of operative excision in each of these cases is indicated. The simple broken line indicates the removal in Case 6 (control).

said that his arm had been definitely stronger and more agile since the operation. He believed that the sensory deficit had not been altered by operation.

Examinations (H. H.).—Left upper limb¶: There was normal strength, and only fine movements of the fingers appeared to be lost. There was slight atrophy of the interossei. There was marked hyperextensibility of the limb. Tendon reflexes were hyperactive. The hand was held fingers apart, with the fingers placed at different levels.

Sensation. Sensation to pinprick was diminished over the entire left upper limb, mostly over the palm of the hand. Light touch was not felt in that region. There was a definite deficiency in two-point discrimination, in point localization, in dermographia, and in position sense of the fingers. Heat and cold were felt normally.

There was astereognosis with complete inability to differentiate the qualities of material (ahylognosia). He had difficulty in identifying spatial qualities (dysmorphognosia). There was a clear extinction phenomenon to pinprick over that limb.

Left Lower Limb: Muscle strength was normal, but the segment could be hyperextended. Tendon reflexes were increased, but there was no Babinski sign, and no alteration of sensation save a slight modification of position sense in the toes.

Face: No facial paresis but a slight deficiency in two-point discrimination over the left side of the face.

Visual Field: The left upper quadrant seemed to be affected in single confrontation tests.

Speech: Emissive or receptive speech, writing, and reading all seemed normal.

Praxis: No ideational or ideomotor apraxia. No apraxia for meaningless movements.

Constructive Praxis: Simple flat models were well drawn either on command or from a copy. But difficulty appeared at once when he copied a house with need for perspective; he completed the task very slowly, after much hesitation, and the impression of perspective was very poor. Similarly, when copying a cube, he began correctly but could not articulate the different lines about the first square in order to create an impression of volume. His first attempt was left unfinished. He finished the second one, but, even though he had a model that he had manipulated a great deal and followed religiously, his drawing did not give one a feeling of depth (Fig. 10*B*). This was also evident in more involved drawings. He could not draw a star on command because he could not join the various angles together. He succeeded only partially with a model.

His drawing of a man (Fig. 10*C*) was very poor and very childish. His joining the upper limbs to the body was inadequate, and, on the right side, he had to try many times. When trying to draw a bicycle from memory, he found it impossible; he outlined the two wheels, but then he stopped; he wondered how it was done and gave up. He sketched a copy of a model but could not join the various portions of the frame together, and he remarked spontaneously: "It is the distance between the parts that I cannot reproduce" (Fig. 10*A*). Building with sticks was much better, with or without a model; and he was able to make a cube and a house with perspective. With a model he could rebuild a triangle with interlocking pieces quite rapidly.

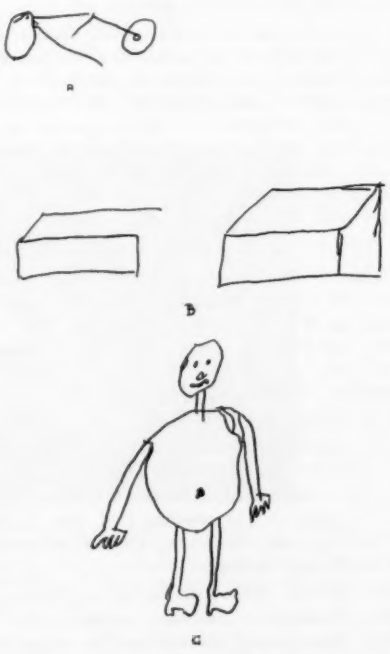

Fig. 10 (Case 3).—*A*, attempt to copy a drawing of a bicycle; *B*, attempt to copy a drawing of a cube; *C*, drawing of the mannikin to command.

Dressing Praxis: He stated that he had never had trouble with dressing, even immediately after operation. Yet he admitted it was sometimes difficult for him to tie his necktie. He succeeded in front of a mirror, but he had to concentrate intensely. Without the help of a mirror, he failed before us. He kept on turning one of the ends around the other, having finally no material left to slip through the knot. He thus made a ball wherefrom no end escaped. He blamed this on his clumsy left hand, although this hand had been used only to hold one of the ends.

¶ The hand area in the postcentral gyrus had been removed, but not the arm area.

Body Scheme: Knowledge of his body seemed to be intact. He recognized right from left very well, both on himself and on the examiner. No finger agnosia.

Visual Gnosis: He recognized objects, colors, images, geometrical figures, and symbols well. He identified rapidly the four objects of Poppelreuter's test. Spatial gnosis was not disturbed. His orientation was very satisfactory, both in the hospital and in the city. Relief and relative or absolute distances of objects were gauged accurately. The diagram of the room was well done. However, he was somewhat inaccurate in placing the main cities on the map of Canada. No unilateral spatial agnosia was detected in the test or in ordinary life.

Arithmetic: Reading and writing figures were well performed. He added well but made mistakes in multiplication, although he wrote down the figures correctly and applied the principle involved. His mental arithmetic was bad as soon as he had to subtract. He numbered objects without fault and rapidly, whether they were placed on a line or spread about. He read the time well. He had a good sense of rhythm and of the passing of time.

There was no abnormality of visual coordinates.

CASE 4.—*Gunshot wound of leg (with amputation) and brain injury at 37 years of age; seizures from age of 38; operation at 44—excision of postcentral gyrus for leg only resulted in cure of phantom limb, and excision of parietal cortex with posterior temporal and anterior occipital cortex abolished the seizures.*

This right-handed man, of 41, threw with his left hand but wrote and drew with the right hand. He was admitted May 14, 1948, complaining of focal seizures and of phantom limb pain. Radical cortical excision resulted in arrest of seizures. It also abolished the phantom limb.

On May 20, 1944, while in military service in Italy, he received a shrapnel wound of the left thigh. This required almost immediate amputation of his limb. Six days later, he became confused, disoriented, and somnolent and was found to have left facial palsy, left homonymous hemianopsia, and papilledema. Fat embolism of the brain or a right subdural hematoma was suspected, and a right craniotomy was performed in the military hospital. No further details are now available.

On recovering consciousness, he complained of a phantom limb, which was quite distinct (left leg), and experienced in it bouts of very intense pain. Even then, he noticed that his memory for recent events was very poor and that he had great trouble in finding his way home. Furthermore, he complained of difficulty in reading because the lines blurred, but there was never any impairment of speech.

Seizures made their appearance in August, 1945. At first they occurred two or three times a day, but, with medical therapy, they were reduced to one or two a month. The aura of his attacks consisted of a queer sensation in his head and the feeling that objects were moving very rapidly in front of him. This was followed by a generalized convulsive seizure with unconsciousness.

Examination.—There was an amputation stump of the upper portion of the left thigh, which was not tender when manipulated. There was left homonymous hemianopsia with macular sparing. Otherwise neurological examination was negative. The pneumoencephalogram suggested marked destruction of the posterior third of the right hemisphere.

The electroencephalogram showed slow waves, with a few sharp waves and occasional "spikes," in the region of the right parietal skull defect, with "spike" activity near the posterosuperior portion of this defect.

Operation (June 3, 1948).—Right parieto-occipital craniotomy was carried out with local anesthesia. A dense scar was demonstrated in the parietal and occipital regions. The brain was severely damaged, and over the ventricle in the superior parietal region the brain tissue was almost nonexistent.

A typical minor seizure was produced by stimulating posteriorly and inferiorly in the temporal lobe, the attack beginning with his habitual cephalic aura.

The patient was as much concerned with the discomfort of the phantom limb as he was with the recurring focal seizures. To our great interest, it was found that stimulation of the exposed postcentral gyrus gave rise to a sensation that was similar to his usual phantom-limb feeling.

The electrocorticogram showed abnormalities of potential posteriorly and inferiorly in the parietotemporal zone.

It was decided to excise posterior temporal, parietal, and occipital areas as treatment of the seizures and to remove the postcentral gyrus, or at least that part of it in which the leg was represented, in the hope of abolishing the phantom limb. This excision was carried out (Fig. 11). The excision of postcentral gyrus was complete for the lower extremity and trunk, extending from above downward as far as the portion that corresponded to the contralateral shoulder. The rest of the postcentral gyrus was kept intact, as outlined in the drawing in Figure 11.

Postoperative Study.—Four and one-half years later, in October, 1952, the patient was brought back for exhaustive study by H. H. He had had one seizure only since operation, and the phantom limb had been completely abolished. When asked about the phantom, he seemed surprised and said:

"Oh, it went the way of all flesh." He was a Scot, and his diction was often biblical!

An electroencephalogram on Oct. 6, 1952, still showed some sharp waves and occasional spikes and slow waves, with a maximum amplitude in the right temporal region, although he was free from attacks.

The left upper limb could be hyperextended. The left hand was thinned out, and there was a slight atrophy of the interossei, especially in the first interspace, a finding that may be related to the patient's use of a crutch. The deep reflexes were equal bilaterally. Muscle power was normal except in the fingers, where fine movements were lost on the left side.

There was dystereognosis with amorphognosia (inability to identify spatial qualities) in the left hand, but hylognosis (ability to differentiate the qualities of material) was preserved; position sense was grossly altered up to the level of the elbow.

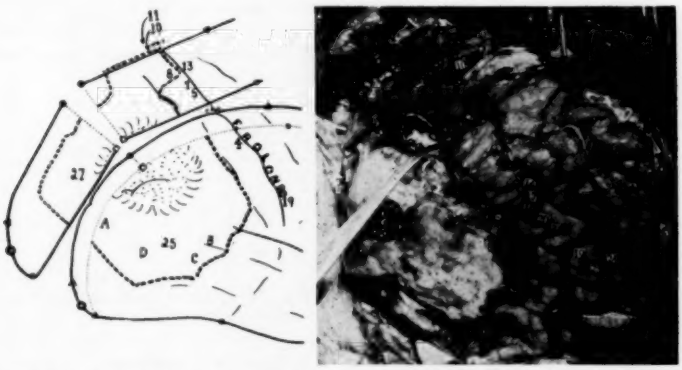

Fig. 11 (Case 4).—On the right, operative photograph after complete excision of the right parietal cortex except for the arm and face area of the postcentral gyrus. The white matter is exposed. The excision of gray matter is outlined in the drawing. The posterior-superior portion of the temporal lobe was thus removed, with very little of the occipital cortex. Numbers indicate responses to electrical stimulation carried out before excision.

Responses were as follows: *4*, sensation in little finger (left); *7*, sensation in left chest; *8*, sensation in "missing knee" of amputated leg; *10*, sensation in missing toes; *11*, sensation in sole of foot; *13*, "something is pulling my stump up," *19*, opening of mouth.

Stimulation at Point *27* produced an after-discharge, while the patient wept and exclaimed, "One of those damned attacks." Electrocorticographic study showed epileptogenic abnormality at Points *A*, *B*, and *C*, as shown in inset.

Two-point discrimination, tactile localization, and letter writing were clearly deficient in the left upper limb. Heat, cold, pain, and vibration were perceived normally. There was no facial paralysis, but tactile discrimination was impaired over the face. Pain was well perceived on the leg stump. Light touch, two-point discrimination, and position sense were grossly disturbed. The extinction phenomenon was evident over the entire left side of the body for all kinds of bilateral stimuli.

There was a complete left homonymous hemianopsia. Language seemed normal except that he tired while reading, since he had to strain to find his lines. It was also difficult for him to write on a straight line.

Ideational and ideomotor praxes were intact.

Dressing Praxis: He mentioned spontaneously that he had had a great deal of trouble in dressing and that he must frequently be helped by his wife. "I get puzzled in dressing. I get my clothes mixed." He said he put his arms in the wrong sleeve of his shirt or he put the back of his shirt in front. This happened even when putting on his pants, in spite of the clue furnished by the short, folded pant leg on the side of the stump. "Sometimes," he said, "I have to fool around till I get it right."

Tieing his necktie was equally difficult. He insisted that he must try many times before being successful. While carrying out this maneuver in front of the examiners, he took the long end of the tie with his right hand and hesitated a long time before twisting it around the other end. Suddenly he tied it correctly and said: "It is a coincidence, a matter of luck. I have to think about it."

Constructional Praxis: It should be mentioned that before being wounded he used to delight in sketching landscapes and that during his professional schooling it was necessary for him to draw outlines of animal or human anatomy, and he stated that he accomplished these tasks perfectly.

On examination, he could draw a square or a cross on command. For a triangle, he made a rectangle. His drawing of a house bore no resemblance to one (Fig. 12*A*). To draw a cube, he tried to proceed in a logical fashion in uniting two squares,

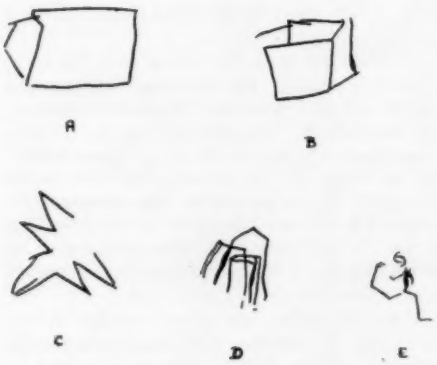

Fig. 12 (Case 4).—Tests carried out four and one-half years after operation. Drawings executed without models.

A, a house; *B*, a cube; *C*, a star; *D*, a swastika; *E*, a mannikin.

but he was unable to connect them properly (Fig. 12*B*). He could not draw a star or a swastika (Fig. 12*C* and *D*). For the latter, he could only make some vertical and horizontal lines, while he attempted verbally to describe the orientation of its various projections. He copied a zigzag or a swastika fairly well, though he did not reproduce accurately the inclination of the lines of the model. Copying a cube required meticulous observation of the model. In his copy of a house he forgot the left side (Fig. 13). His copies of a star and of a bicycle show that he is incapable of articulating the different parts and of reproducing the proper proportions (Fig. 13).

He could build simple models with sticks accurately. When building a house with perspective, his construction was fair except for a certain deviation of the angles. He was incapable of building a cube and could only place one square beside the other (Fig. 14). In copying the patterns of the Wertheimer-Bender test, he failed consistently in the complex figures, the elements of which must be joined together, and also in reproducing the correct orientation of the figures. After much hesitation he could put together a simple puzzle.

Fig. 13 (Case 4).—Model and copy of a house, a bicycle, and a star.

Somatognosis: Practically, the patient did not use his left upper limb during the entire examination; it lay, as though forgotten, by his side, with the hand flat on the chair. When his left hand was absolutely necessary for what was required of him, he used it almost normally. Then he sometimes forgot it afterward, leaving it in a cataleptic attitude. When questioned about this, he stated many times: "I am not too sure sometimes that I am aware of this left arm as well as my right."

He said he was completely unable to form a mental picture of his left upper limb with his eyes closed but that he could do a little better when trying to visualize his right upper limb. Right-left

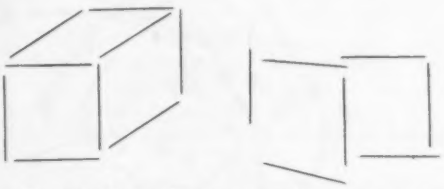

Fig. 14 (Case 4).—Model and copy of a cube executed with sticks.

orientation was performed satisfactorily on himself, but he took a long time in identifying the right and left sides of the observer: "I must turn my body on itself in my mind." He failed utterly when the observer crossed his arms. He could never perform Head's hand-eye-ear test of imitation of the motions of the observer, in which the movements are expected to be done in mirror-like fashion. He could not see the difference between similar drawings oriented differently.

When tested, the patient showed no finger agnosia and no autotopagnosia.

His drawing of a man consisted of simple lines. He said it was "a man in a hurry," and, in fact, one of the legs is raised behind the subject as if the man were running. The head is not joined to the body (Fig. 12*E*). He stated he could not do better. His drawing of a hand had six fingers.

Figuring and Numbering: Writing and reading numbers with many figures were excellent. Mathematical operations were done correctly, but positioning of the figures was poor: The different columns impinged one on the other and rendered figuring difficult (Fig. 15). He could number objects on a

single line correctly; if they were spread about, he neglected those placed on the left.

Visual Gnosis: This function for objects, images, outlines, or geometrical drawings was unaltered. In Poppelreuter's test, he identified three objects but neglected the hammer on the left side. He picked colors out well upon command, and he named them properly. Also, he seemed to be able to visualize objects or colors.

Spatial Gnosis: He could judge absolute and relative distances of objects, as well as depth.

On the other hand, topographical relationships were quite disturbed. When asked to draw an outline of the room in which he was sitting, he understood what was being asked of him, but he could draw only the things which happened to be placed in front of him and to his immediate right or left. Afterward, he was puzzled and said: "I am lost for the other parts. I cannot put the furniture in correct position. I have lost the perception of the

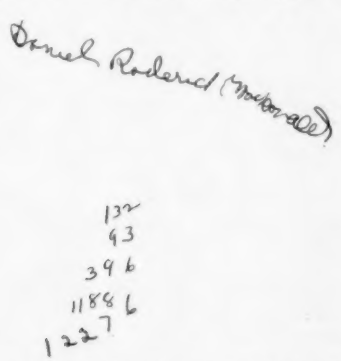

Fig. 13 (Case 4).—Above: example of diagonal writing that resulted despite the fact that the subject was asked to try to keep his writing horizontal. Below: multiplication performed by the same patient. Note the oblique orientation and the commencement of confusion between different rows.

orientation of things." His partial success consisted only in the verbal identification of certain pieces of furniture: "This is on my right; this is on my left." When told to draw the outline of the interior of his own house, he seemed to visualize it fairly well. However, he could not draw it because he could not establish accurate relationships and proportions between the different rooms.

He refused to draw even a simple map. When asked to show where Montreal should be on a map, he pointed to the region of New York. He could not even approximate the position of New York or Chicago. "I am twisted in that."

Unilateral Spatial Agnosia#: This defect was very evident in his behavior, as well as during the test. He said that he frequently bumped against furniture situated on his left when at home and that he tended to walk in circles toward the right and to turn spontaneously to the right, rather than to the left. His neglect of the side was illustrated by his drawing of a house in which the left wall was absent (Fig. 13). When drawing, he tended always to use the right side of the sheet. In Poppelreuter's test he forgot only the hammer, which is on the left. In numbering, he forgot the extreme left.

Topographical Memory: He volunteered that he was unable to find his way even in surroundings which he knew well previously. "I get lost if I go downtown. I cannot find my way anyway if I get out from the seeing of my home. I am completely lost. I don't recognize where I am." He explained that he was not lost as long as he could see his home, but as soon as he turned a street corner he was lost.

He could identify only his own house, and therefore he never went away from home by himself. Though houses and streets might not seem identical to him, he could not draw any references from them; even reading the names of the streets was of little help, since he could not visualize their position in relation to his own house. He could picture mentally the interior or the exterior of his house, but not that of the neighboring houses.

On the occasion of a subsequent visit to Montreal, the patient explained that he had begun to work at the "railroad station" because he could see his own house from there and get home for his meals. If he went "into town," he said, and turned a corner, he would be unable to retrace his steps.

Identification of Faces: He complained spontaneously that he could not recognize people; "I don't recognize anybody till I have seen them a long time." His difficulty in that respect was slight, since he could identify those whom he saw daily. The difficulty may have been due in part to general disturbances of memory. In fact, he stated that he knew he had seen someone before but he was unable to make the connection between a person's name and face. However, he did not associate these faces readily with certain events. For instance, upon his returning from the hospital, the man who worked with him previously came to see him. The patient could not identify him, although he knew that he had been associated with him somehow in the past.

The patient said: "If I meet you in the street in a few hours, I will pass by without knowing you." He knew that there are differences in faces and could not explain his trouble; certainly, faces were not distorted. He knew himself perfectly when looking in a mirror. On a picture of the staff of the Montreal Neurological Institute, he was unable to find Professor Penfield, or even the two doctors who were with him during this interview. Pictures

He had a left homonymous hemianopsia even before operation, as the result of his original injury.

of political figures which, as he said himself, are constantly in the news were not identified, save that of Mrs. Roosevelt, and even then he could not give any verbal description of it.

He was rather vague as to whether he could identify people better from their voice, their figure, or their gait. However, from his own window he knew his neighbors in the streets from the way they walked, though, when meeting them, he did not know who they are. It may be added that when he met one of the examiners on the day following the foregoing interview, he knew who it was from a distance because of the examiner's "general appearance."

Pictures of animals were easily recognized. He said he could visualize clearly his wife's face but not other people's. He could only imagine certain traits, such as a mustache or a bald head, but not the over-all features. He could recognize in an approximate fashion copies of a few works of art. He could take on his face a required expression and also recognize various mimics on schematic drawings of faces or on the examiner's face.

Miscellaneous Tests: Rhythms were reproduced correctly.

Time reading was done well. Time appreciation was erroneous, and he always had an impression of a shorter interval, whether he was tested over a few seconds or over a few minutes. Nevertheless, he was accurate as to the time he had spent in the examining room.

Subjective Disorientation for Visual Coordinates: This was very pronounced: 3 degrees clockwise for the vertical plane and 10 degrees counterclockwise for the horizontal. Writing was very crooked, although it had been stressed frequently that he should try to write on a straight line (Fig. 14). This was also true in drawing and in numbering.

Mental State: He complained of a lack of memory, but it may have been his way of describing the manifold manifestations of his apractognosia. Actually, he was lucid and well oriented and showed good reasoning and a good Scottish sense of humor, as evidenced by his remarks (he recognized immediately the origin of the accent of one of the examiners, and jested: "I guess you are not disappointed by my errors"). Nothing pointed to any degree of mental deterioration. He had a certain amount of culture, and he had worked on the diseases of plants before the war. None of his failures during the various tests had given rise to reactions of catastrophe. He was conscious of them, but he was not unduly concerned about them.

Psychological Note (R. M.; Wechsler-Bellevue Intelligence Scale, Oct. 7, 1952): Body image distortion. A number of qualitative observations indicated distortion of the body schema. "Neglect" of the left side of the body was noted in manual tasks, in which he used his right hand only, instead of both hands, as normal subjects do. Even in the Block Design Test, in which bimanual performance is almost invariable in other subjects, the patient worked only with his right hand. On the Picture Arrangement Test, three of the five pictures in Item 5 were placed on their sides, incorrectly. This is a most unusual error. It was of interest that, in each case, the heads of the figures were placed on the right side. The patient was very slow in the Picture Arrangement Test as a whole.

In putting together the man (Item 1) in the Object Assembly Test, he placed the right leg in first. Although he went on to put the man together correctly, he was not sure, upon completion, whether he had done the task correctly. This feeling of not being sure whether he was correct or not was generally much more typical of his performance on tests involving perception, where he expressed lack of confidence again and again, than it was of his work on the verbal tests.

He put the profile (Item 2) together correctly except for the ear, which he inverted. He failed to assemble the hand (Item 3) correctly. The thumb was the only correct placement. Proceeding leftward from the thumb, his placements were as follows: "ring" finger, "little" finger, "index" finger, and "long" finger. The placements should have been as follows: "index" finger, "long" finger, "ring" finger, and "little" finger. After six and one-half minutes, the patient looked at his own hand, and when the examiner asked him what he thought the puzzle could be, he said that it might be a hand. He was not aware, apparently, that all the fingers were misplaced.

Quantitative data. Like the other two patients (Cases 1 and 2) who were tested with the Wechsler-Bellevue Intelligence Scale, this patient's performance I. Q., of 79, was considerably lower than his verbal I. Q., of 116. This degree of consistency in the quantitative findings appears highly significant and indicates that, generally speaking, impairment is chiefly in the area of perceptual-motor functions.

CASE 5.—*Shrapnel wound of right posterior parietal lobe at age 28; seizures from age 29; operation at age 34. Excision of right parietal and anterior occipital cortex (two stages) in unsuccessful effort to relieve him of seizures.*

This man, of 34, was admitted to the Montreal Neurological Institute on March 14, 1949. He complained of focal cerebral seizures. Operation and radical cortical excision were carried out in treatment of the seizures, and a further excision was done two years later.

In July, 1943, he had been wounded by a piece of shrapnel, which penetrated the right posterior parietal region. The wound produced a left hemiplegia, which disappeared almost completely within a few months. Later on, generalized seizures made their appearance. They were ushered in by a certain

musical sound heard in the left ear and sometimes accompanied by flashes of light on the right side and, more rarely, by a tingling sensation in the left leg.

Upon admission, his examination showed a scar in the posterior parietal region to the right of the midline, with a bone defect of about 2 by 3 cm. The patient had left lateral homonymous hemianopsia and left hemiparesis, which was most marked in the left lower limb. Pain and touch sensations were altered over his entire left side. Two-point discrimination was defective, particularly in the left lower limb. Position sense and vibration sense were also diminished on the left.

The electroencephalogram pointed to an epileptogenic focus in the region of the bone defect, but pentylenetetrazol (Metrazol) activation and photic stimulation were required to bring this out. Pneumoencephalography showed focal cortical atrophy between the right lateral ventricle and the overlying bone defect.

First Operation (March, 1949).—A right osteoplastic craniotomy was performed with the use of local anesthesia on April 7, 1949. Under the bone defect a dense cerebral cicatrix was found extending within the brain and along the falx and including the mesial portion of the postcentral gyrus. Part of this gyrus had been completely destroyed, and the remaining portion, which corresponded to the sensation in his leg, was yellowish in color. The cicatrix was excised together with the surrounding cortex. This included the posterior and medial portions of the parietal lobe.

Postoperative examination showed a left lateral hemianopsia, as well as a diminution of the strength of the left side, as before operation.

Two years later the patient was readmitted, as the seizures had reappeared with much the same pattern, occurring approximately once a month.

Second Operation.—A second right-sided craniotomy was performed on March 22, 1951, and a large further excision of the right temporal lobe and half of the occipital lobe was carried out. The total removal in the two operations is indicated in Figure 9, Case V.

Following this procedure, the general neurological examination was not altered, but the extent of the excision was apparently still insufficient, since the seizures continued at monthly intervals during the next 18 months. The auditory aura had disappeared, but the visual aura continued.

Fig. 16 (Case 5).—Drawings to command. Left: a mannikin; right: a house.

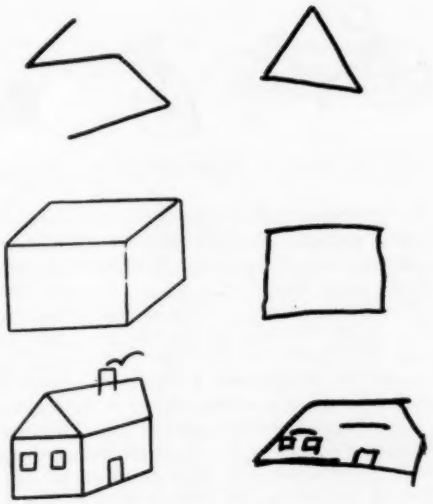

Fig. 17 (Case 5).—Model and copy of a zigzag, a cube, and a house.

Reexamination (October, 1952, by H. H.).—The limbs on the left side could certainly be extended more than on the right. Motor power was slightly diminished in the left foot. Tendon reflexes were more active on the left, but there was no Babinski sign. During the sensory examination, only a slight alteration of position sense in the fingers was found in the left upper limb. Two-point discrimination and position sense were definitely altered over the toes and the ankle of the left side. During bilateral simultaneous stimulation to pinprick there was evidence of an extinction phenomenon over the entire left side of the body except for the face.

There was a left lateral homonymous hemianopsia. There were no disturbances of speech. This patient had not been to school and, although he reads a little, his ability to write was limited.

Praxes: There were no obvious modifications of ideational and ideomotor praxes.

Praxis for Dressing: The patient volunteered that he had difficulty in getting dressed, and this was corroborated by his wife, who must always help him put on his undershirt. He became confused in regard to the legs of his pants while dressing. When told to put on his coat, he laid it out carefully so as to place his left arm in the left sleeve. He explained that he had solved his initial difficulty in that fashion. On the other hand, he tied his necktie and his shoe laces easily. When told to dress his son, he put on the boy's overcoat backward and discovered his mistake only when the child laughed about it.

Fig. 18 (Case 5).—Model and copy of a bicycle.

Constructional Praxes: He could draw a square, a cube, and a cross on command but said he was unable to draw a swastika or a star. He failed completely in the drawing of a house (Fig. 16). One was unable to recognize the model even in his copy of a zigzag. He copied a swastika quite satisfactorily by following the model line for line. Copying a model of a house with perspective produced a marked alteration of all the angles. When copying a cube, he drew only a square (Fig. 17). Upon attempting to copy a star, he drew only the two inferior points and then gave up. When he was drawing the bicycle, his inability to join the different parts was obvious, as was the disproportion between the two wheels (Fig. 18). With the sticks, he could build flat figures and zigzags, but he could not even approximate the house or the cube (Fig. 19). A very simple puzzle was completed only after much hesitation.

Body Scheme: He seemed always to have been normally aware of his left side, and he used his left arm normally. Yet, if he could identify his own right and left readily, he had trouble in doing so on the examiner. This trouble was rectified by turning his own body slightly so as to imagine himself in the same position as the examiner, but he was at a complete loss when the examiner crossed his arms or in the hand-eye-ear imitation test of Head. No digital agnosia and no autotopagnosia was discovered. Though he said that he could visualize his own body when closing his eyes, his drawing of a man was extremely poor and disorganized: Two lines, representing the upper limbs, are joined to a circle, in which three dots take the place of the eyes and nose (Fig. 16).

Spatial Gnoses: There was no impairment of topographical memory. He was well oriented in his home or in his home town. There was no unilateral spatial agnosia. On the other hand, he was totally unable to get oriented on a map, and he could not trace on it even a simple route. On a map of Montreal, after having been told about his own position and that of the mountain, he could not suggest the direction in which the St. Lawrence River should be. He could appreciate distances and relief.

Visual Gnosis: This appeared to be normal for objects and images. He described three objects in Poppelreuter's test. He picked out and named colors correctly upon command. He seemed to be able to visualize in a satisfactory manner. He could identify human faces. Considering his schooling, calculation seemed to be unaffected. Numbering was well performed.

Clock reading was almost always wrong. Apparently, he got the long and short hands confused, possibly because of a right and left disorientation without evidence of any unilateral spatial agnosia (9:15 o'clock was read as 2:45; 10:20, as 3:50).

Visual Coordinates: There was marked deviation from the horizontal, 10 degrees counterclockwise. Vertical deviation was 3 degrees counterclockwise.

Mental State: He was lucid, well oriented, cooperative. His mental level seemed low, but, of course, he had had no formal schooling. He was not working and did not seem to want to work.

Case 6.—*Complete excision of right temporal and occipital cortex (except for convolution posterior to termination of Sylvian fissure). No apractognosia after disappearance of postoperative edema.*

This case (that of a right-handed woman of 32) is added here to serve as a control. The patient complained of focal seizures, and it was soon shown that there was active epileptogenic discharge in the right temporal and occipital lobes. At operation the right occipital lobe was removed, and the temporal lobe almost completely as well (see *Case VI*, Fig. 9).

Before operation she had had difficulty in recognizing faces (agnosia) and some loss of topographical memory, and this continued until postoperative reaction had subsided. Then this difficulty cleared up during the early weeks following operation, and it was concluded that the difficulty had been due to the effect upon the intact parietal area of the local epileptic discharges.

Seven months after operation complete examination for apraxia revealed only some constructional

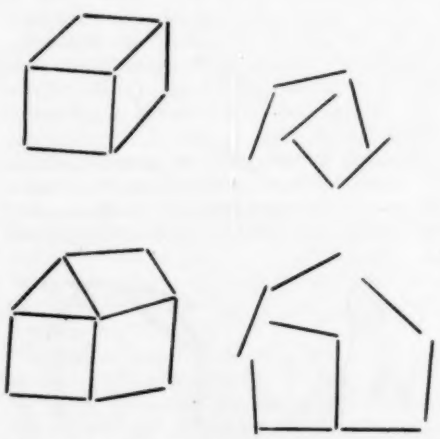

Fig. 19 (Case 5).—Model and copy executed with sticks. Above, a cube; below, a house.

apraxia (inability to reproduce perspective or to articulate the elements of a complex figure). There was also difficulty in maintaining orientation on a map. In addition, she had, of course, a left homonymous hemianopsia.

Two months later, further examination showed that the constructional apraxia had completely disappeared, leaving only slight difficulty in orientation on a map.

It may be seen by reference to Figure 9, *Case VI*, that the excision spared the posterior end of the first temporal convolution. The line of excision must have removed a narrow margin of parietal cortex as it approached the falx. There had been no increase in apraxic defect following this large excision. There never was, in her case, anything comparable to the defects produced by excisions in the other cases, for example, Case 1 (Fig. 1) or Case 4 (Fig. 10).

This suggests strongly that excision of the right occipital lobe and of the whole of the temporal lobe, exclusive of the single convolution next the posterior end of the fissure of Sylvius, produces little, if any, apraxia when the parietal lobe is spared.

3. SURVEY OF LITERATURE (H. H.)

Until now, our knowledge of the right parieto-occipital syndrome has been derived mostly from vascular, traumatic, and neoplastic lesions. Such disturbances as anosognosia or depersonalization for one-half of the body (Babinski, Potzl, Schilder, Pineas, van Bogaert, Lhermitte, Riddoch) have for a long time been recognized as attributable to lesions of the right parietal lobe. Only recently, however, have other disturbances of perception and execution been acknowledged as part of the right parietal syndrome. Dide, Lange, and Potzl, for example, suggested that this region was associated with spatial orientation. Marie, Bouttier, and Percival Bailey classified some elements of the syndrome under the name of planotopokinesia. These authors, however, did not refer the syndrome to a specific anatomical basis. This situation has changed in recent years.

In 1941 Brain [1] studied spatial disorientation and demonstrated the existence of a special form of disorientation occurring in association with lesions of the minor hemisphere and resulting from an agnosia for the left side which is quite distinct from the visual disorientation in homonymous half-fields of Riddoch.[2] Brian also described an apraxia for dressing. In 1945 Hécaen and Ajuriaguerra [3] pointed out for the first time that such an apraxia results from a lesion of the right hemisphere and that it is frequently accompanied by constructive dyspraxia.

In 1944, Paterson and Zangwill [4] reported "spatial thought" deficits following right-sided brain lesions which they claimed were similar to those produced by lesions on the left side. In 1950, McFie, Piercy, and Zangwill [5] described what amounts to the right parieto-occipital syndrome, including the following elements: visuoconstructive disabilities, spatial unilateral agnosia, oculomotor disturbances, right-left disorientation, apraxia for dressing, distortion of visual coordinates, disorders of topographical orientation, and memory. About that time, Hécaen, Ajuriaguerra, and Massonnet * were investigating similar patients and reported six other cases confirming their findings except for the loss of topographical memory. They underlined the importance of the opticovestibular disturbances.

More recently Critchley [8] wrote a complete monograph on the parietal lobes, in which these various problems are thoroughly evaluated. The clinical syndrome had now taken definite shape, but it had not been possible to relate it to a precise portion of this large area.

Body Scheme Disturbances.—These, naturally, are in the fore and include denial of left hemiplegia, lack of awareness of the half-body, a feeling of strangeness, and motor hemiaspontaneity.

The lesion producing such symptoms seems to be located in the inferior parietal lobule (supramarginal and angular gyri), but some workers feel that a double lesion, thalamic and parietal, or a lesion of the thalamo-parietal bundle is necessary to determine such a deficit.

The failure to distinguish right from left, which is part of Gerstmann's syndrome, that is to say, the clinical picture produced by a lesion of the left hemisphere in the corresponding area, can be seen following lesions on the right, generally apart from unilateral

* References 6 and 7.

manifestations. In addition, one must point out that this disturbance may exist only with regard to the outside world. Then the patient is unable to distinguish right from left in the world about him, while he has no such difficulty in regard to his own person.

Apraxia for Dressing.—This defect accompanies hemiasomatognosia fairly frequently. It presents itself isolated from all other apraxic manifestations and is especially marked on the left side. It can also take on another aspect, being then associated with right-left confusion for the outside world. In the latter case, the disturbance is often, but not necessarily, a simple loss of automatic skills, the patient being able to dress himself by referring consciously to the relationship between his body and his clothes. We believe apraxia for dressing means defective awareness of the body and its immediate environment.

This disorder results in faulty application of the clothes to the body and makes it impossible for the subject to work out a clear conception of the body-clothes relationship, or of the symmetrical manipulation of clothes during right-left manual performance (for instance, tieing his necktie or his shoe laces).

Visuoconstructive Disabilities.—These are frequently associated with this second type of apraxia for dressing, and they constitute an important element of the syndrome. The constructive disturbance generally does not manifest itself in simple drawings and constructions reported on a plane, but appears if an element of perspective is introduced. This is in contradistinction to constructive apraxia due to left-sided lesions.

Inability to reproduce a tridimensional pattern, even when the pattern is at hand, seems to be characteristic enough of right-sided visuoconstructive apraxia. The disorder is even better demonstrated during the reproduction of complex figures without perspective: The patient is unable to establish the relationship of the different elements. He cannot give them their normal orientation or establish their relative proportional size. In this respect drawing a bicycle is an excellent test. The Kohs test, which consists in solving a simple puzzle construction, provides equally useful data in this field.

Difficulty in drawing a man may be included among the visuoconstructive disturbances. Dyspraxia and poor knowledge of the body both contribute to this trouble, the latter being at times solely responsible for the disproportion of the drawings. Other psychological processes are involved in the drawing of a geographical map or the diagram of a room.

Disorders of "Spatial Thought" (pensée spatiale of Lhermitte).—These have been stressed by McFie, Piercy, and Zangwill. They isolated the various components which might be disturbed in right-sided lesions of the brain.

1. Loss of conception of topographical relationship (inability to draw a diagram or a geographical map or to orientate oneself on a map)
2. Occasional disturbances of orientation, in which spatial unilateral agnosia plays a part
3. Loss of topographical memory

We consider the first type of disturbance as a prime element in the syndrome presented by many reported cases: Marie, Bouttier, and Bailey mentioned them in their description of planotopokinesia.

Disturbance of orientation is more questionably related to visuospatial gnosic phenomena. Indeed, we believe that this may correspond to a state of clouding of consciousness or unilateral spatial agnosia.

When there is loss of topographical memory, it is conceivable that an associated lesion of the opposite side should be postulated. Unilateral spatial agnosia (visual spatial inattention for the left side) is very frequently encountered in right-sided lesions, especially in more posteriorly located lesions, whether or not the patient is hemianopic. Contrary to McFie, Piercy, and Zangwill, we are in agreement with Brain that it is produced by the same mechanism as neglect for the left half of the body, with which it is frequently associated. The defect manifests itself during constructive or drawing tests, as well as in daily behavior, mainly in orientation. The patient is often unable to find his way and turns constantly to the right.

Disturbances of Calculation and Counting. —Disturbances of calculation have often been reported and related to a wrong arrangement of numbers. Disturbances of counting have also been mentioned and may or may not be due to neglect of the left side. In such a case they could come from oculomotor disturbances.

Opticovestibular Disturbances. — These have been stressed by Hécaen, Ajuriaguerra, and Massonnet: metamorphopsias, sensations of vertigo, inability to write in a straight line, obliquity of drawings, distortions of the subjective horizontal and vertical lines, disturbances of vestibular tests (directional preponderance of a caloric nystagmus).†

The possible role of these disorders which are able to disturb visual perception, praxis, and body consciousness has been discussed.

In summary, the apractognosic syndrome of the minor (nondominant) hemisphere includes (1) disturbances of body scheme (anosognosia or related phenomena); (2) apraxia for dressing; (3) visuoconstructive disabilities, and (4) unilateral spatial agnosia, disturbances of topographical relationship, and, more questionably, loss of topographical memory.

The asomatognosic element seems essential in all these phenomena except the last one. The syndrome might include one or several of these symptoms, this being influenced, partially at least, by a more or less posterior location of the lesion. While localization of anosognosia (disturbance of body scheme) has been supported by sufficiently precise anatomoclinical data, such data are almost completely absent for the other symptoms.

† In this context, it is of interest to recall recent studies of Carmichael, Dix, and Hallpike [9] concerning the effects of cortical lesions on caloric and optokinetic nystagmus. These authors concluded that it was those lesions which involved the posterior half of the temporal lobe and the regions of the supramarginal and angular gyri that were always responsible for a directional preponderance of caloric and optokinetic nystagmus. They claimed, nevertheless, that independent mechanisms subserve the directional control of the caloric nystagmus (parietal) and optokinetic nystagmus (temporal).

4. CASE ANALYSIS‡ (H. H.)

A. Symptomatology. — In general, the apractognosic disturbances were not extreme in our series. Except in two cases, the syndrome was never as intense as that produced by other pathological lesions that might involve structures other than the convolutions of the cortex. The disorders were rapidly compensated by the patients, and fine tests were usually required to demonstrate them. In their daily occupations the patients overcame these disorders in roundabout ways (they used visual clues in order to tie their neckties or copied patterns with piecemeal technique). Many of them were examined long after operation, when the syndrome must have been compensated for; but the tests permitted us to detect the roundabout ways of this compensation.

Be that as it may, the syndrome centers about the visuoconstructive disturbances. As mentioned previously, there is ability to copy or draw spontaneously simple and flat patterns. But the patients fail to reproduce patterns which call for appreciation of perspective, and they are unable to articulate accurately the elements of flat but complex patterns. In two instances the patients expressed their difficulty by saying, "It is the distance of the different parts that I cannot reproduce." Sometimes, this constitutes the entire syndrome.

It has been noted that these patients frequently copy, employing roundabout methods and without understanding the task as a whole. They proceed by slavish copying and by "piecemeal approach," as noted by Paterson and Zangwill.

The examiner's task is also made simpler when the patient is asked to use sticks to reconstruct the patterns rather than to draw them. The manipulation of solid objects seems to call for coordinated visual and proprioceptive data.

Each subject seems to elaborate the motor plan of an act to be accomplished by means of reference to the position of his own body

‡ Cases 1 to 6 have been described in detail. Others in the series have minor references in the text.

in space. Thus, the concepts of superior, or inferior, right or left, are established by the relationships to the subject's body in space. Should he be unable to avail himself of this group of references, or if he does so only by a conscious effort, the graphic disorder will appear unless the visual landmarks are clear enough to guide him.

The patient's awareness of body scheme seems to be made defective by a lesion of the parietal lobe posterior to the postcentral gyrus. This was particularly obvious in Case 1, in which the patient was apt to neglect his left arm as though it did not belong to him. In his case the postcentral gyrus was left intact and the rest of the parietal lobe was removed completely, with the exception of the convolutions adjacent to the sagittal fissure (Fig. 1). Similarly, the patient in Case 4, who had a cortical excision of similar position, but larger posteriorly (Fig. 11), was in the habit of not using his left arm, and, when asked, he stated: "Sometimes I am unaware of this left hand."

The aura described by Case 3 is worthy of note. *"On dirait que le bras s'en va en arrière, qu'il fait de grands mouvements violents derrière ma tête."* (One might say that my arm is going backward, that it is carrying out large, violent movements behind my head.)

Another patient (not described), whose attacks began with discharge in one parietal lobe, stated that for a few days following each seizure she had the impression that her left limbs were shorter. It is obvious that in these four cases awareness of the left body-half was disturbed either paroxysmally or permanently.§

It seems reasonable to postulate poor body consciousness in spite of the gradual clinical disappearance of the disorder in these patients.

Study of the drawn pictures of a man give further evidence of this trouble. Besides poor, childish drawings, these patients showed a striking lack of accuracy in connecting the different segments, a difficulty of articulation. This was particularly evident in Cases 1, 4, and 5, Case D, another case, and, to a less degree, in Case 3.

Body scheme disturbance was shown in another way in Cases 2, 4, and 5, in which the patients were unable to distinguish right from left in the surrounding world. Case 2 had also slight difficulty in pointing to fingers. In earlier examinations in Case 1 the examiners found a slight, but definite, difficulty in finger gnosis, as well as difficulty in pointing on command to different parts of the patient's or the examiner's body.

If right-left confusion forms part of the syndrome of minor-hemisphere lesions, at least with regard to the surrounding world, finger agnosia has been described only following lesions of the dominant side. In a recent review of the literature, Lunn found no exception to this rule, an apparent one being due to a bilateral lesion or to ambidexterity. In Case 2 there may have been a certain degree of bilateral involvement, since there existed a questionable impairment in deep sensation on the right side and a generalized dysrhythmia in the EEG.

In Case 1, with right posterior parietal lesion, there was no question of bilaterality of the lesion, and there was no ambidexterity. Although this difficulty in finger gnosis was practically absent the last time the patient was examined, its persistence a year after the operation raises the possibility of a certain degree of finger agnosia produced by a right parietal lesion.

As usual, we have found apraxia for dressing to be closely related to body-scheme disturbances. In Cases 1 to 5 both defects were present, although in varying proportions. In Case 3 the patient had minimal difficulties in tieing his necktie. But this was corrected with the help of vision. Case 1 reported that his difficulty in dressing disappeared rather quickly and was thereafter present only when he dressed in a hurry.

B. Spatial Orientation and Topographical Memory.—The unilateral spatial agnosia so frequently encountered in patients who suffer

§ It is possible that the local epileptic discharge affected the postcentral gyrus in the latter two cases, whereas the excisions spared the postcentral gyrus in the former two.

from lesions of other types was rarely seen in this series. Most of our patients presented slight evidence of such a disability.

In Case 6, for example, the patient did not close the right side of her drawings and forgot in the reconstruction of a puzzle a small piece to her extreme left. Only in Cases 1 and 4 was there a definite disturbance of this type.

Case 1 had a tendency to refer stimuli in the left visual field to the right. The fact that errors in the past-pointing test were evident only with the left hand and for objects situated in the left visual field may also be considered as evidence of unilateral spatial agnosia. On scrutinizing the results of a code test (Digit-Symbol Test of the Wechsler-Bellevue Intelligence Scale, administered 101 days after operation) we were interested in finding that the patient's failure seemed to be explainable on this basis, too. His main difficulty seemed to be that of entering the symbol in the box to the right of the correct one. He frequently forgot to cross his t's. The tendency to neglect the left space is definitely accompanied by a lack of motor spontaneity of his left side. At the dinner table he used to keep his left hand in his pocket and eat only his meat because he said he had not noticed the vegetables habitually placed on the left side of his plate. He also stated that he frequently bumped into people and objects that happened to be on his left. This, of course, may be explained by the fact that he had a partial left homonymous hemianopsia.

Case 4 also bumped into furniture placed on his left side, always turned to his right, did not complete the left side of drawings even when copying, and neglected to count the objects on his extreme left in the test.

Even topographical relationships were not found to be markedly impaired. Three patients exhibited difficulties in orienting themselves on a map, but this may have been due to other mechanisms, especially right-left disorientation. In Case 5 the lack of education must be taken into account. In Case 4 knowledge of topographical relationships was extremely disturbed. He could not orientate himself on a map. His comment was: "I get twisted in that." He was unable to place Chicago or New York on the map of North America and could not draw the diagram of the room.

All these patients except Case 2 could appreciate depth or relative and absolute distances quite well. Case 2 complained of his inability to estimate distances while walking, especially when climbing steps. His mother had noticed that he would miss a chair when seating himself, having misjudged his distance from it.

Topographical Memory Disturbances: These were definite in Case 6 during the preoperative and immediately postoperative periods and permanently in Case 4, favoring the opinions of McFie, Piercy, and Zangwill, who related these manifestations to right-sided parieto-occipital lesions. It is fair to mention that the excision in Case 6 (Fig. 9) was temporo-occipital and impinged only a little on the parietal lobe, and, further, that after the excision and subsidence of epileptic discharge in the parietal cortex the disability disappeared. However, in Case 4 the loss of topographical memory produced by the ablation (Fig. 11) was so intense that, years later, the patient could not take a walk alone out of view of his own house without losing himself.

Therefore, as far as the evidence from these two cases is concerned, we must conclude that right-sided lesions, which involve occipital cortex alone, produce little, if any, disturbance of topographical memory. There must also be involvement of the right parietal cortex, and perhaps posterior temporal cortex, if topographical memory is to be lost.

Disturbances of Calculation and Counting: These were also rare. The trouble experienced in Case 2, and to a slighter degree in Case 3, could be attributed to the parietal syndrome in spite of the fact that these defects were not of the spatial type. In fact, poor use was made of mathematical concepts. In Case 4 there was no real disturbance in calculation, but the order of the numbers in the different operations was very distorted,

much like the disturbance described by Marie, Bouttier, and Bailey as an element of planotopokinesia.

Directional and Vestibular Disturbances: These disorders were not predominant, but trouble of visual coordinates appears to be pretty constant, judging from the cases in which we were able to look for it. As a rule, it was moderate, the deviation being of the order of 2 to 4 degrees, and more in the vertical than in the horizontal plane. Three patients found it impossible to write in a straight line. In Cases 4 and 5 the difficulties were very marked. During the postoperative examinations it was impossible for Case 4 to keep his writing on a straight line while drawing, writing, or calculating. The deviation of visual coordinates was 3 degrees for the vertical and 10 degrees for the horizontal one. The same was true in Case 5.

Oculomotor Disturbances: None were demonstrated in these cases. The recordings of ocular movements did not show positive abnormal results except in occipital lesions, and these were not accompanied by manifestations of the syndrome under discussion.

No disturbances of time appreciation, rhythm perception, or reproduction were discovered.

Visual Gnosis for Images as Objects: This was not disturbed in these cases. This observation is in accordance with the usual findings in cases showing an agnosic syndrome resulting from right-sided lesions.

Case 6, and, to a less extent, Case 4, bring up the question of the relation of prosopagnosia, that is to say, the agnosia for human faces as the result of right-sided lesions. This would deserve a lengthy discussion. Recognition of human faces as an isolated visual agnosia has been reported very seldom in the literature.[10] The association present in Cases 6 and 4 of topographical memory troubles and prosopagnosia has already been emphasized (Wilbrand, Hécaen, Ajuriaguerra, Magis and Angelergues, Klein). Some manifestations in favor of a predominantly right-sided lesion, especially parieto-occipital, such as the existence of left hemianopsia, transitory anosognosia, neglect of the left half of external space, and disturbances of time perception, have also been reported in several cases of agnosia for human faces.

The right-sided localization of the lesion in Cases 6 and 4 deserves to be emphasized, suggesting prosopagnosia as a possible element of the apractognosic syndrome of the minor hemisphere. But the nature of the lesion and the presence of contralateral EEG abnormalities in Case 6 and the slighter extent of the trouble in Case 4 must make one hesitate to draw a final conclusion.

C. Localization.‖—Having discussed the clinical symptomatology, we shall now consider the problem of its correct localization. It is noteworthy that our cases provide particularly good material for such study, since the limits of each excision were ascertained with considerable precision.

First, we must point out that in our "positive" cases there was always a large removal, mainly parietal but also extending posteriorly and inferiorly. In all these cases the parietotemporo-occipital junction was involved in the excision. When we superimpose on a single brain chart the outlines of the removals in eight cases in which the syndrome was definitely present, we find overlapping in an area involving the gyrus supramarginalis and partially the gyrus angularis and the posterior part of the first temporal convolution, that is to say, Areas 39, 40, and 22 of Brodmann, or 7a, 7b, 22, and the anterior part of 19 of the old Montreal Neurological Institute brain chart. In Figure 20 the outlines of excision in eight cases are superimposed.

Case 6 was not included, since the lesion in this case took in only the inferior and posterior part of the area described above and her symptomatology was more visual, and only transitory.

In fact, the area thus delimited cannot have an absolute value, especially with respect to the angular gyrus. Its role should not be minimized, in view of the findings

‖ There will be further discussion of this subject in a later section of this paper.

in other series. One must note that the partial elimination of this area from our series depends only on the limits of the cortical excision in a single case (Case 3). We can only say that for the presence of the right-sided apractognosic syndrome, the parietotemporo-occipital junction must be affected, at least in one of its portions.

It is of some interest to recall that Blum, Chow, and Pribram [11] argue that the posterior neocortex, exclusive of its sensory projections, should be treated as a whole in the macaque. These authors had made large lesions of the posterior part of the cortex, destroying most of the temporal, occipital, and parietal lobes. They produced in this way a definite loss of visual discrimination in the macaque, which was specific for this type of excision. However, it is fair to add that the destruction of a small area of the temporal lobe (the ventromedial surface) gives a similar result.

From our knowledge of the localization of left-sided lesions producing the apractognosic syndrome (Gerstmann's syndrome, constructive apraxia), one can see that analogous, though not identical, functional values can be ascribed to the symmetrical region of the minor hemisphere.

Lesions of the anterior and superior portions of the parietal lobe are not capable of producing any part of this syndrome alone. There must be involvement of the parietal cortex that passes over into temporal and occipital cortex. But when both are destroyed, it is possible that the former may modify the clinical picture a little. The evidence in Cases 4 and 5 suggests that damage to this whole region may favor the appearance of directional disorders in the clinical picture. On the other hand, in four patients with an excision either anterior to the supramarginal gyrus or in the superior parieto-occipital region, no apractognosic signs could be elicited, and it seems reasonable to exclude the superior parieto-occipital region from this syndrome.

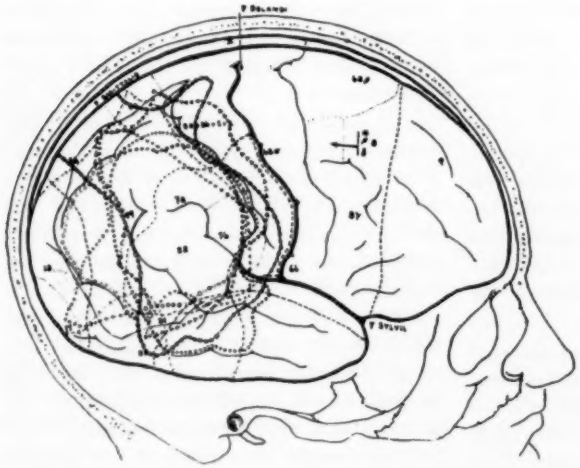

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Fig. 20.—Outlines of cortical excisions carried out on the right hemisphere of eight patients, all of whom showed the syndrome of apraxia and agnosia.

D. Negative Cases.—Let us consider, now, the other negative cases, i. e., those in which the location of the lesion would have led one to expect positive symptoms.

To start with, when one examines the negative or slightly positive cases, one can state definitely that the younger the patient at the time of the excision or the earlier in the patient's life the causative lesion appears, the less marked the functional disturbance that results from the removal. Such

early lesions may cause displacement of certain types of function and allow substitution for others.

What about the left-sided excisions in the two left-handed patients (a limited excision in the first one, yet involving the posterior parietal area; a very large excision in the other)? No apractognosic symptoms could be detected in either of these patients. The mother of one of these patients stated that before the accident, which occurred at the age of 18 months, the baby showed a preference for the right hand.

It is clear that there was no representation of speech function in the areas removed or in the adjacent convolutions, since no aphasia occurred during attacks or during operative stimulation or in the period of postoperative convalescence.

There were no apractognosic symptoms during the convalescent period either; so one may conclude that speech, as well as hand dominance, had found a localization elsewhere because of the lesion. But the area did not serve the usual function of the minor hemisphere either.

In anatomoclinical cases, such as those of Hermann, Potzl, and Nielsen, a right parietal lesion produced Gerstmann's syndrome, together with an agnosia for the left side, while in Brain's case dysphasia, dysgraphia, and dyslexia were combined with unilateral spatial agnosia. Such cases indicate that a single hemisphere may assume the two functional specializations at the same time.

Humphrey and Zangwill's [12] analysis of the findings in a left-handed person with a lesion of the right hemisphere shows the existence of symptoms usually found in a lesion of the minor hemisphere, together with signs of impairment of the major hemisphere. The marked recovery in their case led them to conclude that right-hemisphere dominance in these cases was not established as firmly as left-sided dominance usually is in right-handed persons. Finally, Zangwill ¶ has recently reported a patient with a left-sided parietal glioma, producing slight aphasia, some trouble in calculation, visuoconstructive difficulties, and dressing apraxia.

In contrast to our two patients (in whom left-handedness was related to old lesions of the left cerebral hemisphere), each of Zangwill's patients wrote with his right hand. Zangwill believes this explains why the patient with a lesion of the right hemisphere did not suffer from agraphia, while the one with a lesion of the left hemisphere did. In the latter, he argued, the mechanism subserving writing had been organized in the left hemisphere in spite of his left-handedness. These cases suggest a true dissociation between various functions and cerebral dominance, as postulated by Nielsen and by Brain.

The extent of the excisions is of considerable importance. It is only in those cases in which it is quite extensive and centered around the area described above (Fig. 20) that such a complete syndrome is encountered (Cases 1, 2, 3, and 5, another case, and especially Case 4).

In one of our negative cases (not described here) the whole right parietal lobe except the postcentral gyrus was included in the removal without producing this syndrome. But a large atrophic lesion had been produced in the right occipital and parietal lobes by a serious infection at the age of 6 months. Later, when the focal epilepsy was treated, the occipital lobe was removed, and 18 months later the whole parietal lobe except for the postcentral gyrus was excised. This patient, who was definitely right-handed and an excellent witness, did not experience any gnosopractic disturbance, even immediately following either of the surgical excisions. It seems likely that the early lesion in this case had already produced the functional shift toward the other hemisphere.

In general, when discussing apractognosia, in the positive cases, and the lack of it, in the negative cases, one should remember that functions such as consciousness of the body, visual recognition, or praxis must depend in part on the manner of their original establishment. This may produce indi-

¶ Zangwill, O. L.: Personal communication to the authors.

vidual differences. Often, also, an affective factor cannot be excluded.

Not all of us have acquired the knowledge of our body in the same way. Perhaps the proprioceptive data are dominant in some, the visual data in others. A lesion which disturbs visual components might be expected to produce the apractognosic syndrome in persons of the visual type but would not affect one of the motor type. At all events, patients seem to show different ways of compensating for their defects.

5. AURAS AND SENSATIONS (H. H.)

It was decided to review some of the Montreal material to discover what light might be thrown upon the problem of apractognosia by cortical stimulation and localized cortical epileptic discharge. Since Hécaen and Ajuriaguerra [7] had made a previous study of this question elsewhere, it was H. H. who undertook the Montreal review.

It should be pointed out, however, that the surgeon (W. P.) had made no previously planned study of the practognosic function of the minor hemisphere, and therefore such observations as were recorded at the operating table had been blundered upon, without regard to the problem, in the course of routine explorations and treatment.

In this section, therefore, we turn our attention to those modifications of a patient's awareness of his body during focal cortical seizures. We may also consider similar "opticovestibular" or visuovestibular phenomena, hoping for further understanding of the apractognosic syndromes.

This study will be described under three headings:

A. Body scheme auras (somatognosic)

B. Sensations of movement produced by stimulation

C. Visuovestibular phenomena produced by stimulation or during auras

A. The Somatognosic Auras

Such auras are less rare than might be supposed. Recently, Hécaen and Ajuriaguerra [7] reviewed this problem and added 32 personal cases. The sensations reported include feeling of absence, feeling of bodily modifications (size, shape, and weight), hallucinations of motion, phantom limbs, and heautoscopia. The localization of the lesion could be verified in only seven of these cases. The lesions are grouped in two regions: One is anterosuperior, in the superior part of the postcentral gyrus or even on its mesial surface; the other is situated at the level of the inferior parietal lobule. Lesions in the former produced somatognosic auras concerning the inferior limb, while those in the latter involved the superior limb. In one of these cases, stimulation of the floor of a post-traumatic cyst during operation (Dr. David) produced the aura, which was a sensation of absence of the contralateral hand.

In a review of the charts of patients operated upon by one of us (W. P.) five cases with somatognosic auras due to right-sided lesions, and three of such auras due to left-sided lesions, may be added. A description of the spontaneous auras, as expressed by the patients themselves, follows:

Patient A says that he does not know where his arm is or states that his arm feels "out of place . . . as though someone has twisted it behind my back or up behind my neck or to the left."

Patient B states that he feels a strange sensation in his left hand; it is almost indescribable: a sort of feeling of numbness or pins and needles or immobility or clumsiness or that that hand increases in size. After the beginning of twitching of the left side of the face, there follows the feeling that "it was pulled upward, off into space."

Patient C states that the aura was a feeling that the left half of his body (face included) was "wiped out," "emptied," that it was "absent or not there," though he knew it was still present. He experienced minor seizures consisting of a sensation of the left side of his body as though it had "perished," this being accompanied by clonic movements of the left superior limb.

Furthermore, in Case 3 minor attacks of this kind followed operation, as already described.

Finally, Patient D experienced after her attacks the feeling of having a shorter left arm and leg.

In these five cases, the feeling was localized in the left side of the body and resulted

from a right-sided lesion. Unfortunately, stimulation at operation did not reproduce the typical aura. However, the cortical electrical abnormalities pointed to the posterior parietal or temporoparietal region.

The following three observations are worthy of note, for the patients had spontaneous somatognosic auras involving the whole body or the limbs on both sides and the epileptogenic lesion was left-sided.

Patient E felt that all his body was straightened, as though lying above his bed. He said that he tried to place his arms on either side of the bed to prevent a fall. However, his wife stated that no such movements occurred.

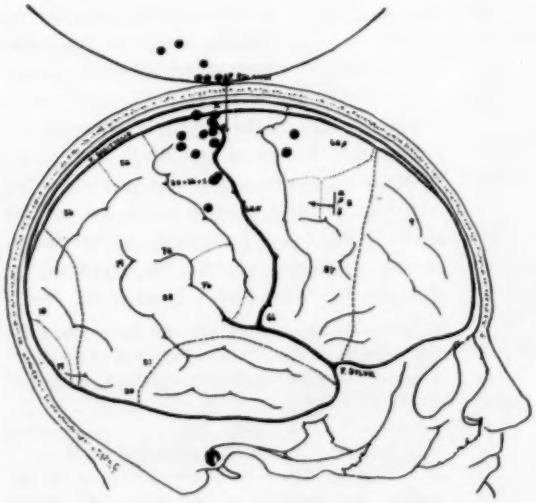

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Fig. 21.—Sensation of movement. The small black discs show the localization of points stimulation of which gave a sensation of movement in one of the contralateral limbs. Review of operation records by H. H.

Patient F had a feeling of fullness, as though all his body had become large and blown up.

Patient G experienced sometimes, among other auras, a numb feeling involving the whole body and the sensation that both feet were extremely swollen.

In these cases no exact localization of the focus of origin is now attempted, except that the area was in or about the parietal lobe. The five right-sided lesions produced somatognosic auras involving the left side of the body only. This is probably only an evidence of discharge in the postcentral gyrus, to judge from the stimulation experience of one of us (W. P.). But the auras referable to the whole body that were described in the three cases of left-sided lesions must have other localization.

B. Sensations of Movements Produced by Cortical Stimulations

Sensations of movements are not exceptional. Penfield and Erickson,[13] and later Penfield and Kristiansen,[14] stated that these sensations were produced by stimulation of the postcentral gyrus, while the urge to move more frequently followed stimulation of the precentral gyrus. Penfield and Rasmussen [15] examined the production of these sensations of movement more extensively and found that, although they were more frequently observed in stimulations of the postcentral gyrus, they were sometimes produced in the precentral gyrus as well.

We have now reviewed many of the stimulation charts in which a sense of movement was produced and summarized the points of stimulation in Figure 21. All these patients, except one, reported a sense of movement only when the postcentral gyrus was stimulated in the arm or the leg area.

The description of the sensation given by the patients was usually that they felt movement in a limb when no movement was seen by the observers. In two cases the

feeling was more elaborate: One patient reported that his knee was turning around and around. Another said that his leg was moving and floating. They had the impression that someone was moving the limb. In two cases the sensation of movement was accompanied by paresthesiae in the involved limbs (as if "asleep," or a feeling of "looseness").

It is an unexpected finding that all these sensations of movement of the contralateral limb were produced by stimulations of the

C. Visuovestibular Manifestations

Penfield and Kristiansen [14] reported that vestibular phenomena were encountered as auras in patients with lesions affecting primarily the posterior and inferior portions of the temporal lobe and the temporoparietal regions.

Penfield and Rasmussen [15] stated that stimulation points producing equilibratory responses were located chiefly in the first temporal convolution, the sensation being primarily that of movement of the body.

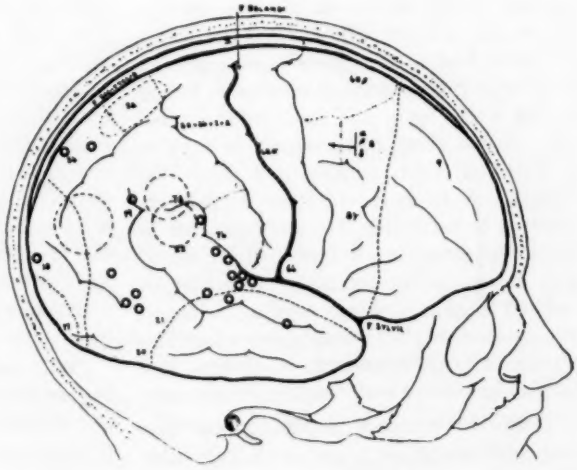

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Fig. 22. — Opticovestibular or visuovestibular responses. The small circles show the position of stimulations that produced these responses, and the large circles or ovals, the probable localization of auras of this type. Review by H. H. of large number of operative cases.

right hemisphere in right-handed patients. We have already seen that Case 3 had a spontaneous aura of this type after the right parietal lobe had been removed together with the postcentral gyrus. The attack was due to discharge in the precentral gyrus, and the peculiarity of the patient's accompanying sensations may have been due to the absence of the cortex behind.

On the other hand, however, in auras of this type, Hécaen and Ajuriaguerra [7] did not find this lateralization. The feeling of movement involved the left side in only 7 of 13 cases. The same is true of other published cases.

They reported that occasionally these sensations were obtained by parietal cortical or subcortical stimulation, but no analysis of the reports for other areas of the cortex was attempted.

H. H. reviewed the case histories of the patients operated upon by W. P. during a 10-year period to find such auras reproduced by stimulation or localized by EEG and sensations produced by stimulation which may be of interest here.#

The results are summarized on a brain chart, as shown in Figure 22. The different

Further reference is made to stimulation results in Section 6.

points at which auras were produced or responses to stimulation of an equilibratory nature occurred are indicated. Visual illusions in which vestibular components are evident (moving of objects distorted or oscillating contours) are also included. As shown in Figure 22, it might be considered that there are two groupings of response points. The first one, anterior and inferior, on the first temporal convolution; the second, posterior and superior, scattered across the posterior temporal and parietal lobes.

In studying the sensations experienced by these patients, one notes that the phenomena are not at all similar in the two groups. Of seven patients whose response points fell in the first location, three noted expressly that they felt a sensation of rotation or falling of the whole body, and three others stated that objects about them seemed to turn in a stated direction without any other disorientation. In only one case did objects seem to be oscillating. Of seven patients in the second group, none expressed the sensation of rotation of the body. Two had an isolated illusion of things rotating, while in five cases such phenomena appeared as distortion of lines, movements of objects, isolated or associated with rotatory components.

Thus, the evidence might suggest that vestibular auras or auras with vestibular components can be divided in two separate groups: one, with a lesion in the posterior portion of the first temporal convolution, in which lesion a purely vestibular character predominates; the other, more posterior, in which the visual phenomena are more frequent.

6. NOTE ON LOCALIZATION (W. P.)

The results of cortical excision in the right hemisphere, as summarized here, confirm the general conclusion that a lesion of the area, which is roughly delimited as the parieto-occipitotemporal junction, gives rise to the apractognosic syndrome. In our cases the important area, in this regard, seems to surround the posterior end of the fissure of Sylvius, being made up of parietal and temporal, rather than occipital, cortex. Superficial removal in this area produces the disturbances of the "body scheme" which seem to be at the root of this manifestation.

In cases of cortical excision, such as those on which this study is based, the surgeon's aim is to remove by suction the gray matter of the convolutions which are living and at least partially functional but which are epileptogenic, and to leave intact the underlying white matter, as is shown in the photographs of Figures 1 and 11. He tries, as best he can, to leave the circulation and connections of the remaining convolutions untouched. Indeed, the success of such surgical procedures depends upon the careful preservation of all gyri not removed, so as to avoid further scars of gray matter.

Thus, although he does not always stop the attacks completely (alas!), he does succeed in leaving normal function in the surrounding convolutions without cutting their connections to the integrating systems of the thalamus and brain stem. It seems evident that these cases provide more reliable localizing evidence than those in which the brain destruction is produced by tumor growth, trauma, or vascular accident.

From the point of view of localization, Figure 20 shows the outlines of eight cases of minor-hemisphere cortical excision, superimposed on one brain chart. The supramarginal gyrus, if it is understood to include the convolutions that surround the lateral cerebral fissure (which we shall call by the long familiar name of fissure of Sylvius), seems to form the center of it.

If we make reference to the cases described in detail in this study (Cases 1 to 5) and the outlines of the excisions in each of these (Figs. 1, 6, 9, and 11), it will be seen that the area that has been shaded in Figure 23 is common to them all. The shaded area may be too large, but it includes the cortex and transcortical connections, a lesion of which may produce the syndrome of apractognosia.

In Figure 1 (Case 1) and in Figure 11 (Case 4), as well as in Figure 9 (Case 3), the excision did not include the parietal convolutions which border the longitudinal fissure, and yet the syndrome was still pro-

nounced in Cases 3 and 4 four and five years, respectively, after removal. There had been a large degree of improvement in Case 1 during the six years that preceded final examination.

The postcentral gyrus was likewise preserved, except for the leg area in Case 4 and the face and hand area in Case 3. Case 2 (Fig. 6) had only a small postcentral-gyrus removal in the trunk area, and Case 5 (Fig. 9) had no involvement of the postcentral gyrus whatever.

The occipital cortex was not removed in any of these five cases, although involvement

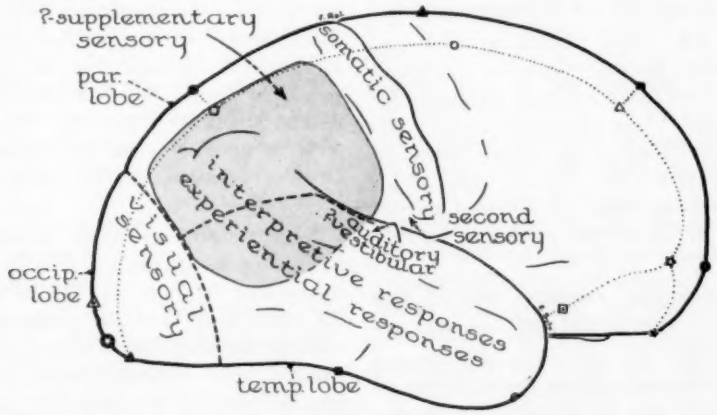

Fig. 23.—The zone of right parietotemporal cortex in which the lesions of this series have produced the apractognosic syndrome has been shaded on a brain map.

Functional areas, as outlined by W. P. in other cortical stimulation studies, are also indicated on the map to show relationship: somatic sensory, visual sensory, auditory sensory (Heschl's gyrus within fissure of Sylvius), vestibular sensory (?), second sensory (superior bank of fissure of Sylvius), supplementary sensory (?) (within sagittal fissure), interpretive psychical, and experiential psychical.

of the optic radiations resulted in varying degrees of homonymous hemianopsia.

It is interesting to observe that about this shaded area, which seems to be devoted to awareness of body scheme and spatial relationships, the principal cortical sensory areas are distributed. We have indicated in Figure 23 the localization of sensory functions in the posterior half of the cortex of man. These sensory boundaries are drawn from the work of others and from the evidence provided by cortical stimulation and local epileptic discharge which has been detailed elsewhere, especially by Penfield and Rasmussen [15] and by Penfield and Jasper.[16]

It is apparent, then, that the shaded area of cortex is bounded by the somatic sensory area on the postcentral gyrus, in front; the visual area in the occipital cortex, behind, and the auditory and vestibular areas, below. The auditory area is much larger than can be indicated on the map, as it extends inward and backward to a great depth within the fissure of Sylvius, where it occupies the anterior transverse temporal gyrus, or gyrus of Heschl. The extent of the vestibular area has never definitely been delimited.

There are other areas where stimulation may produce somatic sensation: the second sensory area, which begins on the superior lip of the fissure of Sylvius, at the foot of the precentral gyrus, and extends inward and posteriorly on the superior bank of the fissure of Sylvius, and the circular sulcus deep to that.

Hidden within the longitudinal fissure there is still another somatic sensory area encircling, and extending posterior to, the Rolandic foot area. It may be called supplementary.

The second sensory and supplementary sensory areas have, each, a bilateral body representation, although responses to stimulation are more frequently contralateral.

The same is true of the visual cortex. That portion which is located on the lateral surface is secondary, as contrasted with the banks of the calcarine fissure, which is primary and gives contralateral responses; and the stimulation causes the patient to see lights or colors or darkness in either field of vision or in both. These zones of sensory responses—somatic, visual, auditory, and vestibular—encircle the area of cortex that seems to be essential to a patient's awareness of body scheme and spatial relationships.

On the other hand, stimulation sometimes does produce positive results in the lateral surface of the temporal lobe and posterior parietal lobe. These are responses of a different order. They are psychical, instead of simple sensory. The region from which such stimulation results are obtained extends back into the area that is shaded in Figure 23.

These psychical responses are of two types*: (1) experiential and (2) interpretive (Penfield [17]).

We would conclude that the syndrome of apractognosia may be produced by absence of the cortex that is bounded by the sensory areas indicated in Figure 23, without direct involvement of these sensory areas and without removal of the most superior and mesial portion of the parietal lobe. Further study may well serve to show that the extent of the shaded area should be decreased.

The parietal, occipital, and temporal lobes are separated by arbitrary dotted lines in Figure 23. The frontier of the occipital cortex may be easily and clearly established by cortical stimulation in conscious patients. As stimulation is carried forward across the occipital cortex, the visual sensory responses stop suddenly at the frontier, and complicated psychical responses appear instead. There may be a narrow zone, demonstrated between the two, where stimulation produces scintillation or vibration of objects seen.

But there is no sharp functional boundary to be found by such methods between temporal and parietal cortex. It is possible that the shaded area should not extend as far across as it does, into the temporal cortex. It is possible, perhaps, that the shaded area should be pushed over into the longitudinal fissure somewhere. But this Figure must serve to summarize our present conclusions as to localization, derived from the cases presented.

Negative evidence might be added here from surgical experience. Excision of the cortex that encircles the shaded area does not seem to produce the syndrome, but it must be admitted that we have not studied patients after operation with the special attention given to this matter by H. H.

On the other hand, in a long series of temporal lobe removals, which include the anterior 5 to 8 cm. of the lobe, careful psychological study has been carried out by our associate, Dr. Brenda Milner.† Her observations indicate that after right temporal lobe removal a postoperative defect in the patient's spatial abilities sometimes appears, whereas in removal of the left temporal lobe, anterior to the speech areas, there develops only a corresponding defect in verbal ability. In neither case is there anything that could be called frank aphasia, on the one hand, or anything to be compared in magnitude to the apractognosia seen in

* In the experiential response (or epileptic aura) the patient is suddenly aware of a previous experience (psychical hallucination). This, it is thought, may be produced by neuronal conduction from the point of stimulation to ganglionic areas, at a distance from the electrode, where the detail of conscious experience is stored. The interpretive response consists in an alteration in the patient's interpretation of the meaning of present experience, which may seem suddenly familliar, strange, or silly. Sources of sound or sight may appear to him to be nearer or farther away, larger or smaller. He may feel himself alone, out of this world, or afraid.

† Milner, B.: Intellectual Effect of Temporal Lobe Damage in Man, Thesis, McGill University, 1952. This paper will be elaborated in a subsequent publication.

the temporoparietal cases reported here, on the other.

7. GENERAL COMMENT

Even though we emphasize the importance of the somatognosic disturbances as the central element of the syndrome of apractognosia, we are not attempting to assign such a function to a definite structure. We do not even feel that a somatognosic function should be thought of as an isolated entity, any more than the "sense of space" or the "function of visualization." The individual develops such capacities by the constant integration and utilization of many functional areas. The peculiarities of the training and experience of one person, as compared with those of another, might well produce individual variations in the functional organization of this area of the brain.

In addition to the localization of lesions which cause disturbances of the perception of space relationships or body scheme, one should consider how the patient, with his lesion, is experiencing his defect, exteriorizing it or compensating for it, and by what means he is doing so.

The syndrome of the right parietal lobe must vary a good deal, according to whether the lesion is placed more anteriorly, inferiorly, or posteriorly. Involvement of the postcentral gyrus results in loss of cortical sensibility in the opposite limbs, including the sense of position of those limbs. If the lesion is entirely posterior to the postcentral gyrus, cortical sensibility is spared. Isolated removal of the second somatic sensory and supplementary sensory areas, shown in Figure 23, produces no sensory defects that we have been able to detect. The same is true of the "secondary" visual areas (extracalcarine occipital cortex). Homonymous hemianopsia appears only when the calcarine cortex is involved or the visual radiation is interrupted as it passes through the temporal lobe. Lesions of the auditory and vestibular areas alone in one hemisphere produce no obvious functional defects, auditory or vestibular. It is possible, however, that a lesion in the posterior parietal and temporal region may have a different functional effect upon the patient when these dispensable neighboring sensory areas are simultaneously involved as well. This combined effect may be surmised, but there is no evidence available, as yet, to prove it.

In any case it is clear that the posterior parietal and temporal area, which is included in the shaded area of Figure 23, has an important interpretive function to discharge, a function which has, in it, elements that are proprioceptive, visual, and perhaps vestibular. It seems to play an integrative role that makes possible normal awareness of the left side of the body and of the body's relationship to the external world.

There is a strange difference, which is not easily understood, between the functions of the two parietal lobes. A lesion in the parietal area of the dominant hemisphere produces bilateral body-scheme disorders, either localized to the fingers (finger agnosia) or generalized (autotopagnosia). On the other hand, a lesion in the minor parietal area disturbs the body scheme unilaterally.

Ideational and ideomotor apraxias form a part of the clinical picture due to left-sided lesions. The apraxia for dressing is met with only in right-sided lesions. The visuoconstructive disabilities are integral parts of both the right and the left syndrome, and the exact difference between these two types of constructive apraxia is not yet clearly established.

The question of spatial gnosic disturbances is still controversial; only unilateral spatial agnosia and defects of topographical relationships can be definitely attributed to right-sided lesions. In both cases the mechanisms are nearer those of somatognosic disturbances than those of pure visual agnosias. The view that loss of topographical memory is a syndrome of right-sided lesions is perhaps not proved, although two of our cases favor this hypothesis.

Nevertheless, it is not as yet possible to attribute spatial agnosias to lesions of the right occipital lobe in a definite manner, or image and object agnosias to lesions of the left lobe. One can only be sure of the fact that spatial orientation is disturbed

especially from right parieto-occipital lesions, that is to say, that the processes not specifically optic, but, rather, opticovestibular, are disturbed especially in right-brain lesions. As for prosopagnosia, our cases suggest that it originates from right-sided lesions, but more data are needed to prove this point.

Faced with such a functional specialization of each parietal lobe, we are at a loss for a satisfactory explanation. The most striking fact is that, while a lesion of the minor hemisphere produces change in awareness of the contralateral side, one in the major hemisphere produces bilateral disturbances. The few cases of right anosognosia due to left-sided lesions were found, it seems, in ambidextrous patients.

Could we assume that somatognosic disturbances referable to one or the other hemisphere differ only in their topographical distribution? No, indeed, since the behavior of the patient is very different in the two cases. While the hemiasomatognosic or anosognosic patient has forgotten his body-half or denies his hemiplegia and behaves as if his defect were absent, the patient with finger agnosia or autotopagnosia is aware of his body but simply does not grasp the relationship of the position of its different parts unless, of course, a general intellectual disturbance is also present. In brief, the disturbance is recognized in the latter case. It is unconsciously incorporated in the general thinking in the former.

The importance of the dominant hemisphere for language is well known. A possible hypothesis is that in all cases of body-scheme disturbances resulting from dominant-hemisphere disease there is a concomitant speech defect, latent or evident. The following facts are reasonably certain: (1) Language and body scheme are intimately related; (2) the motor tools for language, as well as its perception, are located bilaterally. It is then fair to say that there is some degree of bilateral representation of somatognosia. The part of the dominant hemisphere subserving somatognosia must surely have close connections with the speech areas.

At the very highest level of integration, we think not in terms of the half-body but in terms of the body as a whole. The experiences produced by integration of sensory data are primarily one-sided, but during verbalization experience enters the sphere of concepts and symbols and a half-body has then no reality. Only the body as a whole can be conceived as a point of reference in our dealings with the outside world.

If a lesion is produced in the major hemisphere, the connections between body scheme and language will be dissociated once more in varying degrees; but traces of the connections persist and continue to modify the effects of dominant-hemisphere lesions, so that the picture presented is different from that of the minor hemisphere.

The patient is still able to integrate the primary experiences from his half-body and is aware of it, but the precise relation between language and body scheme is lost and he cannot name or point to the various parts of his body on request.

On the contrary, in the minor hemisphere, the experiences are organized without the help of language, from data coming from the opposite side, and the connections are limited to those subserving immediate awareness of the contralateral half of the body.

We would like to stress that in epileptic auras, when brevity prevents any attempt at reorganization, lesions of the dominant hemisphere will sometimes produce a contralateral asomatognosic manifestation, though much less frequently than in lesions firing from the minor hemisphere. Hécaen and Ajuriaguerra [7] have observed personally or collected from the literature 51 cases of right-handed patients showing unilateral body-scheme auras; in 15 of these the aura involved one or both right limbs. We feel that the instability of the disruption of linkage between language and somatognosia is all important in determining the aype of aura from lesions of the dominant hemisphere. It is in such cases that we find unilateral body-scheme disturbances as a result of disease of the dominant hemisphere.

8. SUMMARY

The apractognosic syndrome resulting from lesions of the right cerebral hemisphere includes a group of manifestations related to alterations of somatognosia. In addition to body-scheme disturbances of the anosognosic type, there are visuoconstructive disabilities, apraxia for dressing, difficulties in spatial orientation (unilateral spatial agnosia, disturbances of topographical relationship), and alteration of visual coordinates. Loss of topographical memory is also a probable constituent of the syndrome, although possibly still a disputable one. This syndrome has been found in parieto-occipital lesions of varied etiology.

The evidence presented in this study provides a clearer indication of the cortical areas, the absence of which produces the syndrome. In studying patients who had undergone cortical ablations to stop focal epilepsy, we have found the syndrome to be present in varying degrees in nine cases. In all these cases the parietotemporo-occipital region was involved. The tracing of the lesion in eight cases (Fig. 20) includes, as a common ground, the supramarginal gyrus, part of the angular gyrus, and the posterior part of the first temporal convolution.

In the sixth case (control), the symptoms were produced before operation, as a result of the functional disturbance associated with the epileptic state. The whole of the occipital lobe and all of the temporal lobe except the posterior end of the first temporal convolution was excised (*Case VI*, Fig. 9). There was a transient increase in symptoms after operation, followed by their disappearance as the electrographic abnormality subsided in the adjacent parietal cortex. In this case the symptoms were largely visual. In four other cases the excision was anterior parietal or superior parieto-occipital, not touching the above region (Figs. 22 and 23), and no sign of apractognosia could be detected.

Five cases are recorded in detail (Figs. 1, 6, 9, and 11). The overlapping areas of removal in these cases are shown in Figure 23. The wealth of the syndrome seems to increase with the greater size of removal within this zone, and perhaps beyond it. The posterior Sylvian or temporoparietal cortex, in which lesions may produce somatognosic manifestations, lies between the visual, proprioceptive, and vestibular sensory areas of the cortex. The apractognosic symptomatology varies if the lesion extends more anteriorly or posteriorly.

In two left-handed patients excision of the same region in the left hemisphere did not give rise to these manifestations. In another case, no abnormalities were apparent following a right parietal lobectomy (with exception of the postcentral gyrus) in a right-handed person. The possibility of functional shift, due to a destructive lesion early in life, has been discussed above, as well as the relationship of hemispheral dominance to the problem.

In two cases topographical memory was clearly disturbed. These findings support the opinion of McFie, Piercy, and Zangwill on the origin of this disorder.

Results of cortical stimulation of the posterior half of the minor hemisphere were reviewed in the hope of throwing light on this problem. Cortical stimulations of the right postcentral gyrus may produce sensations of movement in the contralateral limbs, and stimulation in the second sensory area may produce sensation of movement or of position in the limbs bilaterally.

Sensations of body movement or movement of the environment, or of change in body position, are often produced in the temporal lobe cortex near the probable position of the vestibular cortical sensory area (Figs. 22 and 23). But visuovestibular (opticovestibular) responses are elicited from the superior parietal lobule as well. They consist mainly in optical illusions (distortions; movement of objects, frequently with a rotary component). No pure equilibratory response was obtained from that region, while in the region of the first temporal convolution sensations of falling or of rotation of the whole body predominate.

Stimulation of the posterior temporal and adjacent parietal cortex sometimes produces

alterations in interpretation of present experience (illusions of distance, size, familiarity, etc.). It may be said that the defects produced by the lesions, discussed above, are defects of perception and of interpretation.

The theoretical implications arising from this study are discussed in an attempt to account for the difference between the somatognosic symptomatology of lesions of the right side and that of lesions of the left side of the brain.

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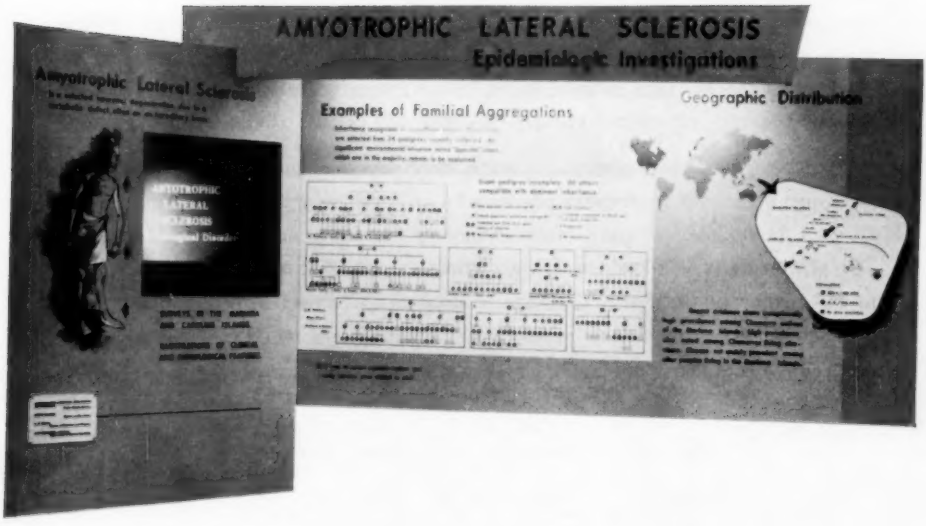
Scientific Exhibits



AMYOTROPHIC LATERAL SCLEROSIS IN THE MARIANA ISLANDS

LEONARD T. KURLAND, M.D., Bethesda, Md.; DONALD W. MULDER, M.D.; GEORGE P. SAYRE, M.D.; EDWARD LAMBERT, M.D., Rochester, Minn.; CMDR. WILSON HUTSON (MC), U. S. N.; LORENZO L. G. IRIARTE, Guam, and HENRY A. IMUS, Ph.D., Bethesda, Md.

THE REPORT of the concentration of cases of amyotrophic lateral sclerosis on the Island of Guam by Arnold and associates (1949) and by Koerner (1952) led to an investigation to confirm the diagnosis and, if possible, to explain this phenomenon. Many of the results of the study so far completed are illustrated in the exhibit.

The exhibit demonstrates the principal clinical and pathological features of the disease in the Mariana Islands and reveals that it is a classic form of amyotrophic lateral sclerosis with a high familial incidence.

Recorded for publication Dec. 12, 1955.

A cooperative effort of members of the National Institutes of Health, Department of Health, Education, and Welfare; Mayo Clinic; Department of the Navy, and the Government of Guam. National Institute of Neurological Diseases and Blindness (Drs. Kurland and Imus); Mayo Clinic (Drs. Mulder [formerly Lt. Cmdr. (MC) U. S. N. R.], Sayre, and Lambert); U. S. Naval Hospital, Beaufort, S. C. (Cmdr. Huston); Government of Guam (Mr. Iriarte).

Shown as a scientific exhibit (with motion picture) of the Section on Nervous and Mental Diseases at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 6-10, 1955.

Permission to reproduce the figures has been granted by the Editor, Proceedings of Staff Meetings, Mayo Clinic, and by the Editor of *Neurology*.

Base-line prevalence data for amyotrophic lateral sclerosis for comparison with the results in the Mariana Islands were obtained from the United States, Canada, and several European countries through mortality statistics and through survey data in Rochester, Minn. It was estimated as 4 to 6 per 100,000 population in these areas. However, the estimated prevalence among the Chamorro people (original natives) in the Mariana Islands, based on an extensive survey of the islands and intensive surveys of selected villages, is about 420 per 100,000 population.

Amyotrophic lateral sclerosis is not unduly prevalent among continental U. S. personnel or natives from other islands who are now living in the Mariana Islands (e. g., Filipino laborers and Carolinian natives who have moved to the Marianas). The prevalence is also low among the distinct groups of Carolinian natives residing in the islands south of the Marianas. Among the Chamorros, 8% to 10% of all deaths in adults are due to amyotrophic lateral sclerosis (corresponding death ratios in the continental U. S., Canada, Great Britain, and Norway are about 0.1%).

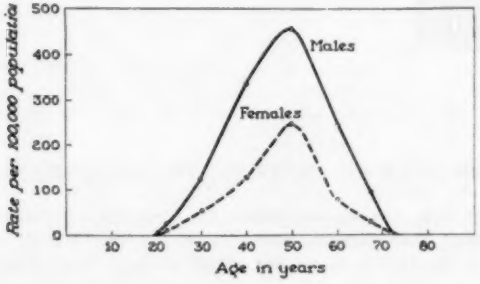


Fig. 1.—Amyotrophic lateral sclerosis incidence rate per 100,000 population on Guam, by age and sex.

Clinically, all cases demonstrate progressive weakness, wasting, and fasciculation of the muscles of the hand or shoulder girdle or bulbar musculature. The course is steadily progressive and invariably fatal, and the classic findings of both amyotrophy and descending motor-tract involvement are found at some time in the course of the disease in practically every patient.

The average age of onset is 44 years, two-thirds of the patients noting the onset of their symptoms between the ages of 35 and 55 years; in all age groups, the rate is almost twice as high in males as in females (Fig. 1).

The duration averages three years; rarely is it less than one or more than seven years.

The course of the disease is not altered by pregnancy.

Electromyographic studies revealed fibrillation potentials produced by denervated muscle fibers and fasciculation potentials associated with muscle twitches. The motor-unit action potentials observed on voluntary contraction were reduced in number and increased in size (Figs. 2 and 3).

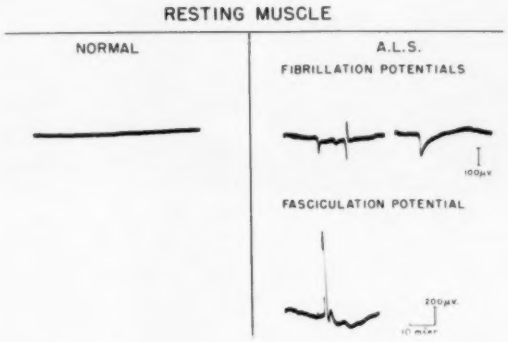


Fig. 2.—Electrical activity (EMG) of resting muscle in normal subject and patient with amyotrophic lateral sclerosis (ALS). Electrical activity of resting muscle is detected by needle electrode and recorded by cathode ray oscilloscope. In normal muscle no electrical activity is detected. In ALS fibrillation potentials produced by denervated muscle fibers and fasciculation potentials associated with muscle twitches are observed. In this and the next Figure, negativity of the needle electrode causes an upward deflection of the oscilloscope beam.

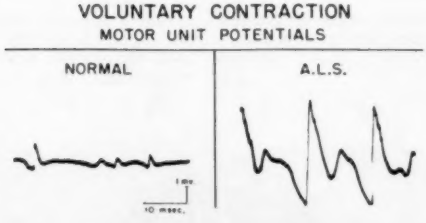


Fig. 3.—Electrical activity of biceps brachii muscle during voluntary contraction in normal subject and patient with ALS. Electrical activity of biceps brachii muscle during voluntary contraction. Motor-unit action potentials are reduced in number but increased in size in ALS.

A large number of central nervous system postmortem specimens have been examined. The classic findings of amyotrophic lateral sclerosis were noted: degeneration and loss of the cells of the anterior horns of the spinal cord (Figs. 4 and 5) and of the motor nuclei of the brain stem and demyelination of the lateral columns, particularly of the pyramidal tracts of the spinal cord (Figs. 6, 7, and 8). Chronic atrophy was noted in muscle sections (Fig. 9).

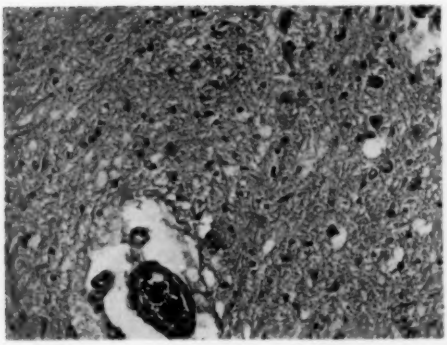


Fig. 4.—Anterior horn of spinal cord of Guamanian patient with amyotrophic lateral sclerosis. Almost complete absence of neurones in anterior horn. Hematoxylin and eosin; reduced from mag. × 190.

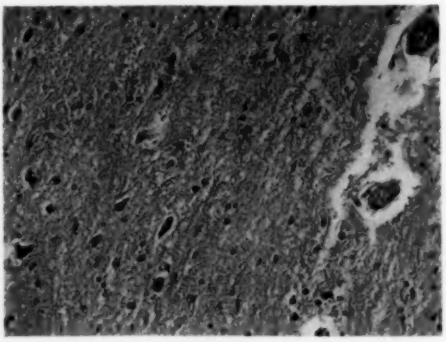


Fig. 5.—Anterior horn of spinal cord of Guamanian patient with amyotrophic lateral sclerosis. Almost complete absence of neurones in anterior horn. Diminished number of anterior horn cells. Hematoxylin and eosin; reduced from mag. × 200.

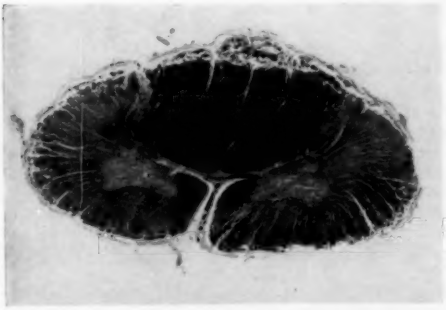


Fig. 6.—Spinal cord. Demyelination of crossed pyramidal tracts in Guamanian patient with amyotrophic lateral sclerosis. Weigert stain; reduced from mag. × 6.

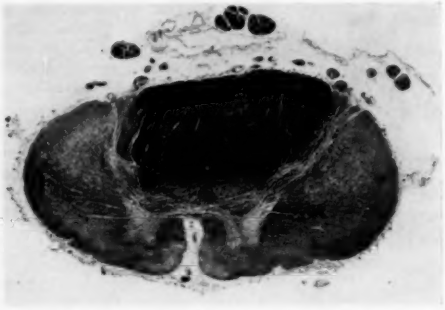


Fig. 7.—Spinal cord. Demyelination of crossed and direct pyramidal tracts in Guamanian patient with amyotrophic lateral sclerosis. Weigert stain; reduced from mag. × 9.

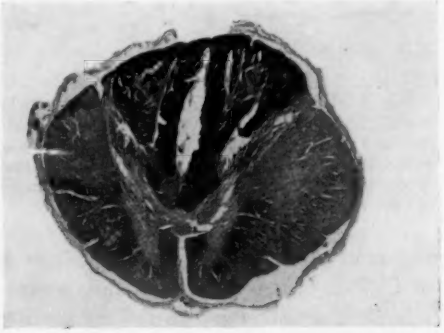


Fig. 8.—Spinal cord. Demyelination of crossed and direct pyramidal tracts in Guamanian patient with amyotrophic lateral sclerosis. Weigert stain; reduced from mag. × 5½.

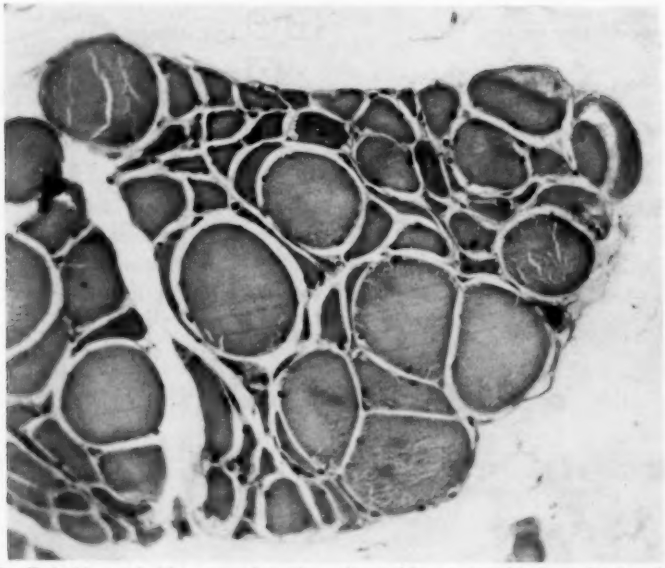


Fig. 9.—Deltoid muscle biopsy specimen in patient with amyotrophic lateral sclerosis showing chronic muscle atrophy (Shy, G. M.; Alvord, H. B., Jr.; Berg, L., and Greenfield, J. G.: Atlas of Neuropathology, figure reproduced by permission of the publishers, E. & S. Livingstone, Ltd., Edinburgh); reduced from mag. × 220.

No arrested or incomplete form of the disease was noted; there was no obvious relationship with any other neurologic or systemic disorder in the islands. The search for possible external etiologic factors to explain the high prevalence in the Mariana Islands has disclosed no obvious environmental difference between the affected and the unaffected. Certain families appear predisposed to the disease (Fig. 10); old native legends and present-day concepts of the natives themselves

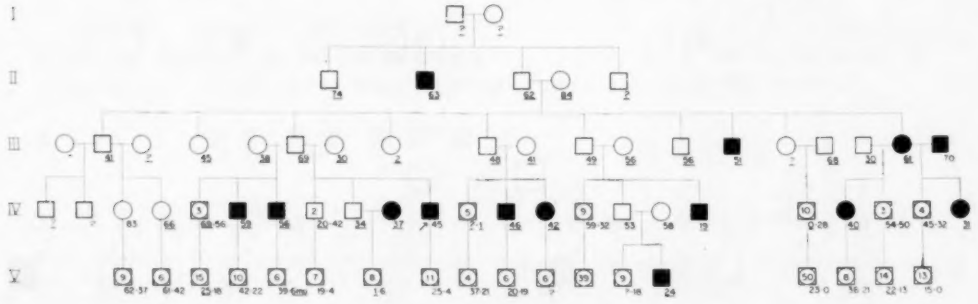


Fig. 10.—J. Q. family, Guam.

maintain that the disease is hereditary. Family histories of the Chamorro patients usually revealed that others in the family had died of the same disorder. Furthermore, some Chamorros were known to have developed the disease even though they had moved to distant lands many years before the onset of symptoms.

As a result of these observations in the Mariana Islands, further studies were carried out in the United States, and a thorough review of the literature for the past 100 years was made. These studies indicated that the long-held belief that

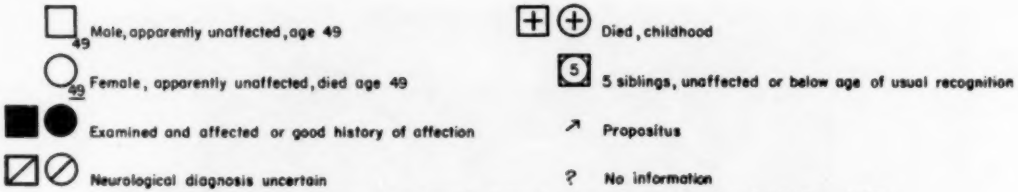

Male, apparently unaffected, age 49
Female, apparently unaffected, died age 49
Examined and affected or good history of affection
Neurological diagnosis uncertain
Died, childhood
5 siblings, unaffected or below age of usual recognition
Propositus
? No information

Fig. 11.—Key to pedigrees, amyotrophic lateral sclerosis (Kurland and Mulder, 1955).

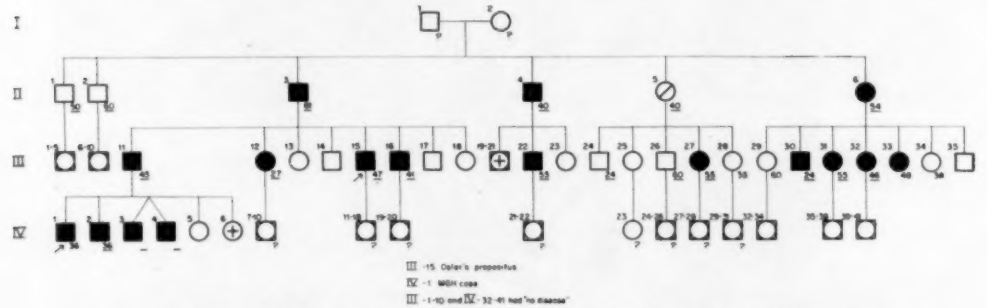


Fig. 12.—Vermont family with progressive muscular atrophy (after Osler [1880] and Brown [1951]; Kurland and Mulder, 1955).

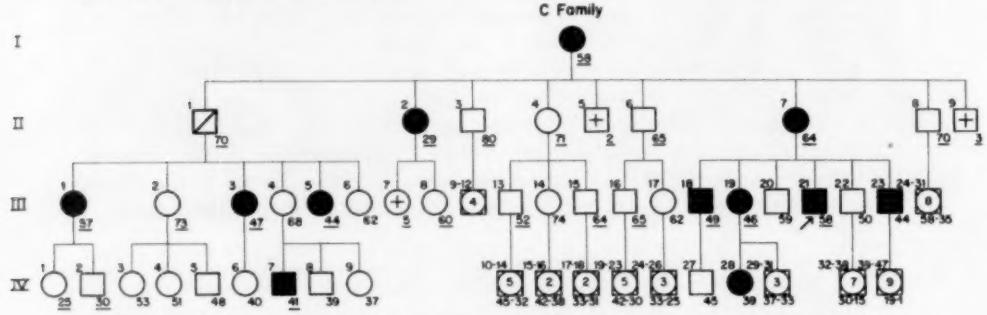


Fig. 13.—C family, Mayo Clinic study, amyotrophic lateral sclerosis (Kurland and Mulder, 1955).

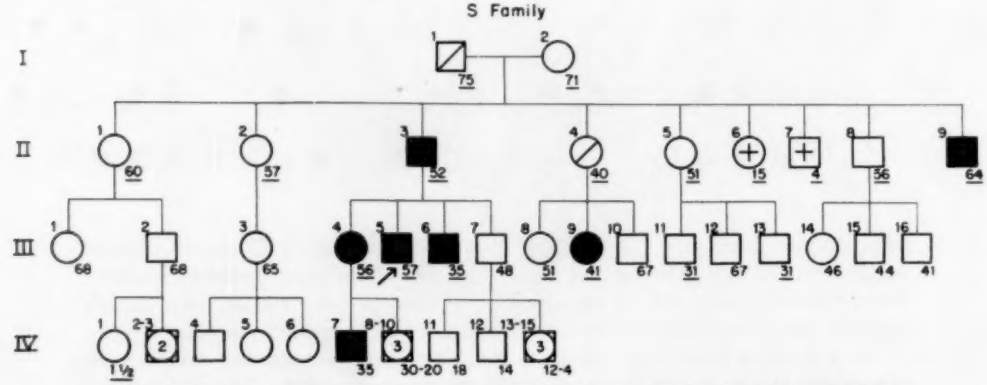


Fig. 14.—S family, Mayo Clinic study, amyotrophic lateral sclerosis (Kurland and Mulder, 1955).

amyotrophic lateral sclerosis is not hereditary may be partly incorrect. Twenty-four pedigrees compatible with dominant inheritance have been collected outside the Marianas (Figs. 11-19). A hereditary form of the disorder, therefore, does exist apparently both in the Marianas and elsewhere. Pedigrees obtained in the Mariana Islands to date, however, are difficult to evaluate because many of the family data are unreliable, and it is still uncertain whether a recessive or dominant mode of inheritance best explains the findings.

Thus, as a result of these investigations, it is hypothesized that an underlying metabolic factor, perhaps often inherited, may be responsible for the degenerative changes which occur so selectively in the motor neurons of the central nervous system in amyotrophic lateral sclerosis.

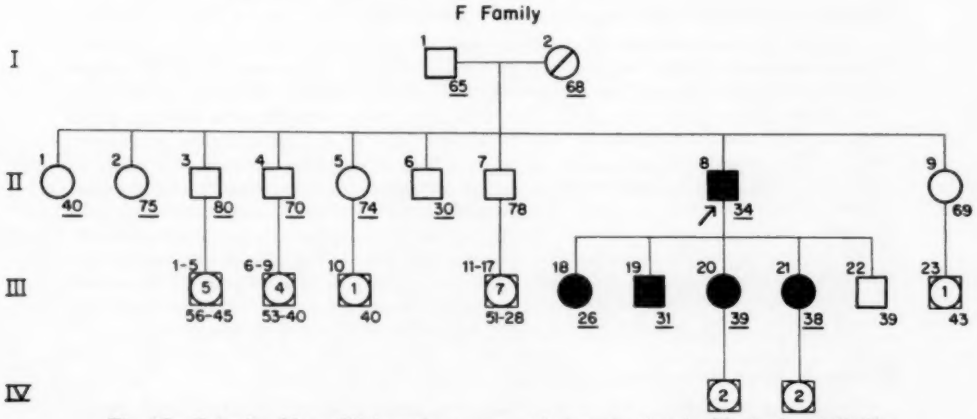


Fig. 15.—F family, Mayo Clinic study, amyotrophic lateral sclerosis (Kurland and Mulder, 1955).

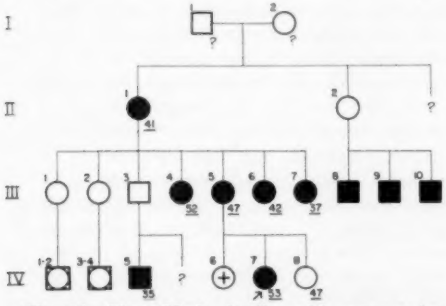


Fig. 16.—New York family with progressive muscular atrophy (after Dana, 1914; Kurland and Mulder, 1955).

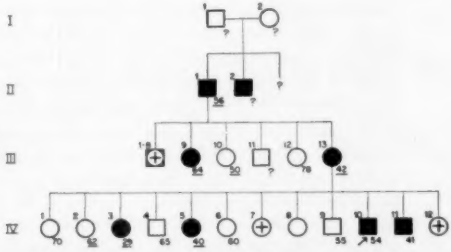


Fig. 17.—German family with amyotrophic lateral sclerosis (after Dittel, 1940; Kurland and Mulder, 1955).

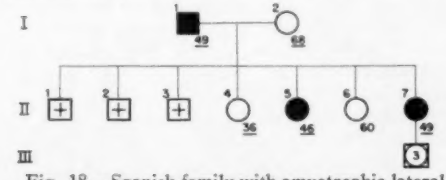


Fig. 18.—Spanish family with amyotrophic lateral sclerosis (after Barraquer-Ferre and Bordas, 1951; Kurland and Mulder, 1955).

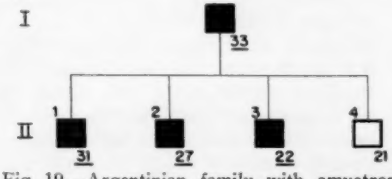


Fig. 19.—Argentinian family with amyotrophic lateral sclerosis (after Montanaro and Lopez, 1931; Kurland and Mulder, 1955).

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Adrien ver Brugghen, M.D., President

Oscar Sugar, M.D., Secretary

Regular Meeting, Oct. 18, 1955

Fractional Pneumoencephalography. Dr. Nicholas Wetzel.

A report of the experiences with fractional pneumoencephalography in 50 cases is presented. The technique used is that of Lindgren. In this method the patient is placed in the sitting position with the head flexed forward about 20 degrees. Five cubic centimeters of air is then injected in the lumbar subarachnoid space and a film of the head taken. With proper positioning of the head, the third and fourth ventricles will be demonstrated. If not, the procedure is repeated after a slight adjustment of the head. When the head is in proper position, further air is injected. In this series it was possible to fill the ventricular system adequately with minimal amounts of air, usually less than 30 cc. Excellent filling of the ventricular system with a minimal morbidity, insofar as headache, nausea, or other symptoms are concerned, was almost routinely obtained. Papilledema is not considered to be a contraindication to this form of encephalography, especially if little or no cerebral spinal fluid is withdrawn. The importance of maintaining a closed system with respect to changing the pressure relationships of the various compartments of the central nervous system is stressed. A series of representative films are shown.

Studies of Adult Brain Cortex in Tissue Culture. Dr. R. S. Geiger.

The present study deals with in vitro cultures of brain tissue obtained from the cerebral cortex of adult rabbits, monkeys, and humans. The selective cultivation of neurons and their maintenance up to eight months in subcultures, and of glia cells is described, and some of their reactions to environmental changes, electrical stimulation, and drugs are demonstrated by time-lapse, phase-contrast microphotography; vital staining, or other staining techniques. In these experiments, it was possible to obtain relatively pure neuron cultures by subculturing the original explant with cortisone added to the feeding solution during the first three passages. If, in the subsequent subcultures (after the third passage), a Tyrode solution extract of brain tissue was added to the feeding solution and cortisone was omitted, the survival time of the neurons in the later passages increased to as much as 16 weeks in the fifth passage, at the time of writing.

A variety of neurons was observed in these cultures, identifiable as pyramidal cells, giant pyramidal cells, giant polymorphous neurons, and bipolar spindle neurons. By the use of Bodian's modified stain (silver protein [protargol] and gold chloride) it was possible to demonstrate neurofibrils in the cell bodies, as well as in the processes of the neurons. With Fletcher's thionine stain, Nissl substance could be demonstrated in most neurons, as particulates, strands, or fine granules. Mitoses of neurons were occasionally seen in subcultures with all the types of media used in these experiments.

Using time-lapse photography and phase-contrast optics, a continuous intracellular activity could be demonstrated in the neurons, consisting of a streaming of cytoplasm throughout the perikaryon and neurites, and a slower movement of cytoplasmic granules to and from the nuclear membrane, as well as to other areas of the cell, such as the neurites. A very slow pulsatile activity of cytoplasm in the perikaryon and neurites was also evident. Staining with vital dyes showed the preference of some granules for Janus green and of others for neutral red, and the accumulation of methylene blue preferentially in neurons. At times nucleolar material could be seen passing from the nucleolus through the nucleoplasm into the cytoplasm. Relatively rapid ameboid movements of glia associated with neurons could be observed. During the migration of the neurons and the outgrowth of their processes, definite patterns of association (synapses) could be established between two or more cells.

After the addition of barbital sodium to the supernatant medium, in a concentration of 20γ per milliliter, the neuron underwent striking intracellular changes. Practically the entire cytoplasm in some neurons, and large areas of cytoplasm in others, appeared to become completely free of granules. About 10-15 minutes after the addition of barbital the granules commenced reappearing. However, they were then much smaller and more uniformly dispersed throughout the cytoplasm. These granules stained vitally with Janus green, indicating that they were mitochondria. After washing the cultures, the mitochondria reappeared in their original size.

After the addition of pentylenetetrazol (Metrazol) in concentration of 200γ per milliliter the cell nucleus changed in size and refractivity, appearing larger and more transparent. The movements of the nucleolus were accelerated, and regions of different refractivity became more evident. In the cytoplasm many granules aggregated into large clumps, and others accumulated in greater concentration around the nuclear membrane. The neurites were more motile and might shorten and become beaded with large clumps of granules. Considerable contraction of the cell occurred. Jacobson's stain, which stains deoxyribonucleic acid and pentose nucleic acid red and purple, respectively, showed that the aggregates in the cytoplasm and the material concentrating around the nucleus contained phosphonucleic acids. The morphological changes observed with electrical stimulation were similar in kind to those observed with pentylenetetrazol.

DISCUSSION

DR. RAY S. SNIDER: It is pertinent to discuss some of the physiological implications of this paper. I was impressed with Dr. Geiger's preparations and think they compare favorably with those from the University of Texas by Dr. Pomerat.

It appears to me that there is an excellent future for this technique, for many years one of the handicaps in neurophysiology was the lack of a technique which would allow one to get to the neuron. This procedure, as outlined in the paper, does exactly that. There is no question that these cells are slightly abnormal. The transection of the axons and the transplantation to a special medium all would certainly indicate some abnormality. However, the response of the tissue, as indicated in this paper, has many of the characteristics of central nervous system neurons.

DR. R. S. GEIGER: Oomura and Takagi, in the anatomical laboratory of the University of Illinois, have started on a program to determine resting and action potentials of these cells in culture. The action potentials obtained using the same microelectrode for pick-up and stimulation ranged from 10 to 20 mv in amplitude and 1 to 2 msec. in duration and had a threshold of 2 to 3×10^{-8} am. The glia cells investigated thus far gave no action potentials. Comparisons are underway on the behavior, reaction to drugs, and cytochemistry and histochemistry of brain tissue from normal and from schizophrenic humans.

DR. R. M. STRONG: Dr. Geiger, have you seen in your preparations the "inclusion bodies" described by Papez in nerve cell bodies from the brains of psychotic patients.

DR. R. S. GEIGER: No special inclusions were found which are characteristic of cells from schizophrenics in the two cases examined at a magnification of × 160 with phase-contrast microscopy. Neurons from all sources may have inclusions.

DR. R. M. STRONG: Papez states that he has seen these organisms in motile stages in vivo with the phase microscope.

DR. R. S. GEIGER: The environmental conditions of neurons in culture are obviously not the same as in the organism. However, the culture medium is controlled as regards isotonicity, pH, and protein content. Of course, the blood-brain barrier is absent. Furthermore, tissue metabolites normally present may not be supplied by the stored blood serum used, whereas others that are removed by the circulation normally may be retained in the medium for longer periods of time.

All available criteria to determine a neuron were employed, such as neurofibrils, Nissl substance, size, and staining properties. In living cells usually a large, round, clear nucleus with a large, single nucleolus, and possibly a nucleolar satellite, is seen. The type of processes, mode of growth, etc., are also significant. Often an axon can be distinguished from other neurites. With vital stains the distribution of neutral-red-staining granules and the preferential uptake of methylene blue by granules in the neurons are also characteristic, as well as the absence of these neurons in cultures of subcortical white matter.

Neurites of cells in cultures may grow or retract and send out new collaterals, as seen by Speidel for nerve fibers in the tail tip of the tadpole. The swelling of the tips of the processes

under the effect of pentylenetetrazol (Metrazol), reported by Speidel, can also be seen in cultures, together with its effect on the whole cell, as described.

Dr. Oscar Sugar cooperated and Dr. Frederic A. Gibbs gave his help in procuring human material and pointed out the many possibilities of further investigations.

Studies in Intracranial Pressure. Dr. Joseph P. Evans and Dr. Adolph Rosenauer.

Adrien ver Brugghen, M.D., *President*

Oscar Sugar, M.D., *Secretary*

Regular Meeting, Nov. 15, 1955

Experiences with Discography. Dr. Beaumont Johnson.

Discography is a useful adjunct in studying low-back and sciatic pain, especially in the patient with an uninformative myelogram. First, the volume accepted by the injected disc indicates degeneration of the nucleus or a rent in the annulus; amounts in excess of 3 cc. are definitely abnormal. Second, a rent in the annulus is confirmed by peridural extravasation of Diodrast. Third, if the pain upon injection mimics the patient's sciatica, it may be significant; it should be evaluated with reservation. However, this latter point and the interpretation of the x-rays are occasionally misleading. The discograms of normal and diseased discs may be indistinguishable. Even with the aid of oblique roentgenograms and stereoroentgenograms, the location and abnormality of a bulge of nuclear material cannot always be determined.

The puncture of the disc is painful and is expedited by heavy premedication. With the patient in the lateral decubitis position and after procaine infiltration, 2⅛ in. #18 spinal puncture needles are inserted in the midline or just alongside the spinous processes at L 3, L 4, and L 5. Their positions are verified by a lateral film and are readjusted when necessary. Four-inch #22 needles are passed transdurally into the nucleus at L 4 and L 5. Diodrast 35% is injected with a three-ring 10 cc. Luer-Lok syringe. Lateral films are taken after each injection; the needles are removed, and finally an AP film is taken.

Twenty-three patients were studied at the Veterans Administration Medical Teaching Group Hospital in Memphis, and 40 interspaces were visualized. The discogram was indicative of pathology in 13 cases and frankly misleading in 4 cases. The diseased interspace was technically inaccessible in six cases, and in three examples, not included here, no interspace could be punctured.

DISCUSSION

Dr. Harold C. Voris: We have done discography sporadically for the past three or four years. I cannot state the total number of cases, but I should estimate it as 15 or 20. I think perhaps the procedure is a little more worth while than Dr. Johnson suggests. Its great disadvantage is that it is of no value for intraspinal lesions. It has more diagnostic value than the speaker suggests, although I must confess, as far as my experience goes, that I have had some trouble in interpreting what you might call the borderline case, where there is some question whether the dispersion of the dye in the intervertebral space is indicative of gross pathology or not. I am sure that before that point is settled a great deal more study will be necessary than is possible from the correlation of the x-rays and the surgical findings in the cases in which an exploration is done.

I confess I do not see much risk or danger of complication. I would be just as willing to have Diodrast in the intervertebral space as Diodrast in the arachnoid space. I am sure there is no more risk than with myelography. The only patient we had with reaction either immediately or later was a nurse in whom myelography was negative but discography showed a protrusion of the fourth lumbar disk. She had several bouts of unexplained low-back pain with sciatica before she was hospitalized. She had an acute exacerbation of back pain and sciatica about 72 hours after discography, and we were concerned about the possibility of infection in the disc because of the apparent incubation period before the onset of symptoms. In view of the severity of her pain, exploration was carried out a few days later. I could see nothing abnormal in the extradural space or in the material removed from the space, no evidence of inflammation or fibrosis; and the pathologist assured me that the tissue removed appeared like the tissue from other discs. So far as our very limited experience goes, there have been no other complications. I think discography will remain of some value in selected cases. After all, myelography, at least in our hands,

as indicated in the paper which I presented before this Society three years ago, has been correct in only 75% of disc protrusions. Our greatest source of error has been in failure to recognize a protrusion later found at operation. The myelogram was negative in these cases, but, because of the symptoms, an exploration was done and a disc protrusion found at operation. Discography may be of value in patients with negative myelograms and clinical evidence of disc protrusions.

Dr. Johnson has described the technique very well. I do not do the examination exactly in that way, but I am sure it is satisfactory in his hands.

DR. BEAUMONT JOHNSON: What histologic study we did on six of these patients showed that the annulus fibrosus appeared the same. Dr. Gardner's series showed no microscopic abnormality following Diodrast. One may note in operating after discography that the disc is more fluid in composition than one usually sees.

Wilson's Disease: A Case Presentation. DR. JOHN S. GARVIN and DR. THOMAS G. BENEDEK.

A 22-year-old woman with tremor and Kayser-Fleischer rings, as well as the biochemical disturbances of increased urinary copper excretion and amino-aciduria, was presented. Moving pictures of this patient before and after treatment with dimercaprol were shown, and the patient herself was present for demonstration of her symptomatic improvement. A brief summary of our changing concept of Wilson's disease was given.

DISCUSSION

DR. THEODORE B. SCHWARTZ: I think Dr. Garvin covered most of the facts available regarding this disorder in his excellent introduction to the presentation of his patient. This disorder was considered primarily a neurologic one until the discovery of high levels of copper in the tissues, when it became, as are many other diseases, a metabolic disorder.

We may divide our discussion into two parts: first, the facts and then speculation. These patients have increased content of copper in the tissues, a decreased amount of copper in the blood, and increased quantities of copper in the urine. Some studies have been done regarding the locus of the copper in the plasma. Apparently it exists in two forms. The first, as Dr. Garvin mentioned, is a very firmly bound copper-protein complex, referred to as ceruloplasmin. This copper does not dissociate from the protein. In addition, there is a more loosely combined form of copper bound to albumin and, to some extent, to α-globulin. This is more easily dissociated. It is this copper that apparently does most of the damage to the tissues.

In patients with Wilson's disease, the concentration of ceruloplasmin is greatly reduced; and, while the copper loosely bound to protein has been found to be either normal or increased, the total amount of copper in the plasma is decreased because of the almost complete absence of ceruloplasmin. The amino-aciduria has been well documented as a constant finding in all these patients. The blood amino-acid levels have been found to be normal. There is one other metabolic abnormality, as to the reason for which I have no inkling; the plasma uric acid has been found to be abnormally low. These are the facts.

How these disturbances lead to disease I do not think anybody can say with certainty. There have been some studies with isotopic copper, measuring rates of absorption and excretion, as well as transport in the plasma. The conclusions that have been arrived at from these studies seem reasonable. The studies referred to represent as yet unpublished work of a former colleague, Wallace Jensen, in Pittsburgh.

It is thought that there may be two defects. One is that these patients absorb an abnormal amount of copper from the intestinal tract. Second, for some reason they are unable to make a reasonable amount of ceruloplasmin. With a decrease of ceruloplasmin there is an increase of copper ion which is circulating, loosely bound, in the blood. This copper ion can be filtered, and for this reason there is an increased amount of copper in the urine. This excess of copper ion can also be precipitated in the tissues. Why it seems to localize in the basal ganglia and in the liver, I do not think anyone has any definite idea. It is known that copper, as Dr. Garvin mentioned, is excreted through the liver into the bile. It may be that excessive quantities are deposited in the liver because of inadequate biliary excretion. It appears that there is some effort on the part of the body to chelate the excess copper with amino acids. If one administers a load of copper, urine copper will increase. Concomitant with this there will be increase in urinary amino acids.

These patients have been treated so as to chelate the copper and increase its excretion. I have followed two of these patients. We used edathamil (Versene) in the treatment, and I think our experience coincides with Dr. Garvin's. It does not provoke any remarkable improvement in liver function but there does seem to have been some suggestion of improvement, or at least arrest, in the tremor that these patients manifest.

DR. BENJAMIN BOSHES: Dr. Garvin, in your review of the literature, what is the youngest age of a patient with the Kayser-Fleischer ring? At the moment I have a patient who is 7 years of age who shows an enlarged liver and other symptoms that are suggestive of Wilson's disease. He is running a high copper excretion, but he still has no Kayser-Fleischer ring, even on the slit-lamp examination.

DR. OSCAR SUGAR: I would like to know what would happen if you fed someone a copper-free diet? Second, is there a sufficiently large statistic to distinguish the benefits of dimercaprol and Versene? Which one would you prefer to use in these cases?

DR. JOHN S. GARVIN: I do not know of any neurologic disease that has a Kayser-Fleischer ring other than Wilson's disease. I agree that the symptomatology is diverse, but I think that when a patient shows an increased excretion of amino acids and copper along with certain neurologic symptoms, one is justified in considering him as having a specific disease entity.

I cannot give you the ages of the patients. One, a patient with pseudosclerosis, was an adult. The other two, with autopsy studies, were adults. There were no children.

In answer to Dr. Sugar's question about a copper-free diet, apparently you can give an essentially copper-free diet. We have given heavy copper diets, and the subjects still have an increased copper excretion.

I do not have any definite feeling about dimercaprol and edathamil; but there were several reports a few months ago of toxic effects from the use of Versene in lead poisoning. I have not used edathamil. I did see a great deal of work with dimercaprol in England about 1950.

DR. THEODORE B. SCHWARTZ: With reference to whether this disease is a disorder of copper metabolism or enzyme metabolism, I do not think that there are data in this disease sufficient on which to base a decision. Someone said, "Man creates God in his image"; and to some God is a great enzymologist.

As to whether it is a disease entity, I should like to point out that there are many possible analogies. It is true that a patient may show nothing but a Kayser-Fleischer ring. However, there are patients with gout who manifest nothing but hyper-uric-acidemia. I do not think this would be a good reason to discard gout as an entity. As we learn more about the disease, the manifestations will be more clearly defined.

Report on the Sixth South American Neurosurgical Congress. DR. PERCIVAL BAILEY.

In this report the papers presented at the Congress were briefly reviewed and commented upon. The neurological institutes in the various countries that were visited were discussed.

PHILADELPHIA NEUROLOGICAL SOCIETY

Axel K. Olsen, M.D., Presiding

Regular Meeting, Dec. 2, 1955

Treatment of Convulsions in Tuberous Sclerosis by Pallidoansotomy. DRS. H. W. BAIRD III (by invitation), H. T. WYCIS, and E. A. SPIEGEL.

A case is presented in which the subcortical origin of generalized convulsions is made highly probable by the cessation of seizures following elimination of an apparent subcortical focus. This 10-year-old boy showed the classical findings of tuberous sclerosis (a butterfly distribution of adenoma sebaceum of the nose and cheeks, intracranial calcification, progressive mental deterioration, and convulsions, up to 250 daily). Since the x-ray studies reveal only a single subcortical calcified nodule in the region of the right caudate nucleus, it was suspected that the seizure discharges might originate in this area, and recording electrodes were inserted in the globus pallidus and the thalamus. Records from these nuclei and the scalp showed spike discharges appearing simultaneously in these regions. The maximum discharges were found in the pallidum. Electrolytic anodal lesions of the area of calcification and of the right ansa lenticularis were produced, using needle electrodes inserted by the stereoencephalotome. In the nine months since operation no convulsions have occurred. Whereas preoperatively the convulsions were

controlled only by excessive, sleep-producing doses of anticonvulsant medication, e. g., phenobarbital up to 180 mg. daily and diphenylhydantoin sodium up to 400 mg. daily, he is now receiving, rather irregularly, 30 mg. of phenobarbital and 30 mg. of diphenylhydantoin daily. Previously he had been a bed patient, but he now walks, runs, follows simple commands, and expresses simple wants.

DISCUSSION

DR. H. T. WYCIS: I would like to demonstrate our Model #5 stereoencephalotome. This apparatus permits one to apply it repeatedly in the exact same position. It is fixed to the skull by means of four screws that carry small steel balls, to which the feet of the stereoencephalotome may be attached in any position. The length of these feet can be varied; on their upper end they are connected to the basal ring by universal joints, so that the base can be easily placed in a position parallel to the plane determined by the Frankfurt horizontal lines. In the basal ring a rectangular frame can be rotated and be moved forward or backward. The electrode holder can be moved on the frame to the left or right and can be rotated in frontal or sagittal directions.

DR. S. F. GILPIN: Is the change in this child's behavior due to the withdrawal of large doses of anticonvulsant drugs? Do you think that he could do without these drugs at the present time? Why are they being continued?

DR. CHARLES RUPP: I would like to ask Dr. Spiegel what a priori thoughts motivated this experiment?

DR. H. W. BAIRD III: I agree with Dr. Gilpin that the improvement of the patient's mental status is at least partly due to the reduction of the medication. Partly it may be due to the cessation of the seizures, since it is known that repeated convulsions, for instance, following electroshocks, may at least temporarily impair the functional activity of the cerebrum. Before operation he had so many seizures that his level of consciousness was greatly lowered. We felt it safest to reduce the medication gradually. Our final goal is to omit the medication entirely. At present he receives only a fraction of his preoperative dose.

DR. E. A. SPIEGEL: The studies presented here are part of a research project which attempts to analyze the role of the basal ganglia in the mechanism of major seizures. Depth electroencephalography is able in some cases of so-called genuine epilepsy to reveal marked seizure discharges in the pallidum, while the scalp EEG hardly shows definite abnormalities. In cases refractory to medical treatment, we tried to influence the convulsions by pallidotomy, and, at least in single instances, a definite reduction of the seizures was obtained. A focus in the striatum influences the cerebral cortex by way of the pallidum in several ways: (1) by pallidofugal impulses to the nucleus ventralis lateralis, from which they are conducted to Areas 4 and 6; (2) by impulses to the nucleus ventralis anterior, which is perhaps part of the diffuse thalamocortical projection system (Jasper); (3) by pallidofugal impulses to the hypothalamus and mammillary body; from there impulses are conducted to the dorsomedial nuclei and then to the frontal cortex, and to the anterior nuclei and then to the gyrus cinguli, respectively. All these striopallidothalamocortical circuits may be interrupted by pallidotomy.

DR. HAROLD STEVENS: In their usual thorough manner, the authors have made a further contribution that not only is interesting as a clinical phenomenon but further documents the theoretical and experimental work of Morison, Dempsey, Penfield, and Jasper on centrencephalic epilepsy.

Cerebral Edema: Studies on Its Location and Mode of Action with Radioactive Sodium. DRS. G. M. AUSTIN JR., R. CORSON (by invitation), J. LINDER (by invitation), R. CHAMBERLAIN (by invitation), and F. C. GRANT.

The role of sodium as a primary osmotic factor in interstitial fluid is well known. We have studied the shift of Na^{24} between brain, blood, and CSF as an indicator of pathways and flow of interstitial fluid. Following intracarotid injection of Na^{24} at operation, brain samples showed the highest content in cases of tumor; next highest in cases of edematous brain. Curves for diffusion of Na^{24} from brain samples into distilled water showed similar rates despite different concentrations. In patients of limited life expectancy who had intracranial operations for malignancy, tracer doses of normal $Na^{24}Cl$ were injected into cerebral white matter. Diffusion coefficients and $t½$ were then calculated for brain, blood, and CSF. These showed an increase in clearance times from a normal $t½$, of approximately 70 minutes, up to a $t½$ of 300 minutes in severe swelling and edema. Clearance was usually more rapid into the blood than into the CSF.

In hydrocephalus it was seen to be reversed, with more rapid clearance into the CSF. These studies suggest that two pathways of drainage of interstitial fluid are both effective, namely, via perivascular spaces into the CSF or by resorption back into capillaries. Under conditions of cerebral swelling and edema, diminished amount and flow of CSF increase the role of capillary resorption.

DISCUSSION

DR. H. A. SHENKIN: I believe Dr. Austin stated that in his cases of cerebral edema the clearance time was markedly prolonged. Is there any reason for this? Is there any connection here with what we know about cerebral blood flow?

DR. H. T. WYCIS: Investigations have shown that vascular tumors show a greater concentration of radioactive substances. In the light of these investigations, can Dr. Austin explain the apparent discrepancy in his material presented?

DR. E. A. SPIEGEL: I have been interested in this problem for years and was able to demonstrate that swelling of nerve fibers is associated with decrease of the double refraction of the myelin sheaths. In these tumor cases, how much was edema, and how much was swelling?

DR. G. M. AUSTIN: In answer to Dr. Shenkin's question regarding cerebral blood flow, our patients showed marked changes in local blood flow. However, generalized increased intracranial pressure, of course, plays a role also. I cannot answer Dr. Wycis' question definitively. One of the reasons for increased sodium retention in the tumor itself, which has always been shown to be approximately three times that of the surrounding brain tissue, is undoubtedly the increase in capillary permeability, so that the sodium tends to leak out more easily. This is due to the necrosis of the capillary endothelium, resulting from pressure of the tumor itself on the surrounding capillary endothelium, and actual necrosis of the capillaries by rapid tumor growth. In answer to Dr. Spiegel's question, Scheinker made an attempt to explain the difference between cerebral edema and cerebral swelling. I believe that, according to his investigation, cerebral swelling is an early and gross stage of cerebral edema. We are now employing histologic techniques in order to confirm our physiologic findings with Na^{24}.

Idiopathic Hypoparathyroidism with Epileptic Manifestations. DR. S. WOLFE (by invitation) and DR. N. S. SCHLEZINGER.

Idiopathic hypoparathyroidism, because of its rarity, may not be thought of in the differential diagnosis of convulsive disorders in children. Furthermore, unless one is acquainted with the vagaries of this disease, the presence of papilledema may make the diagnosis even more difficult. The case of a 9-year-old girl is described in detail. The significant neurological manifestations consisted of tetany, grand mal epilepsy, and papilledema. The laboratory data, including an electroencephalogram, were within normal limits except for characteristic hypocalcemia, hyperphosphatemia, and acalciuria. Following adequate treatment with dihydrotachysterol, calcium gluconate, aluminum hydroxide gel, and a modified high calcium-low phosphorus diet, there was a disappearance of all clinical symptoms, with normal development, during a five-year period of observation. The pertinent literature concerning idiopathic hypoparathyroidism is reviewed.

DISCUSSION

DR. CHARLES RUPP: I believe the author stated that papilledema occurred in 13% of these cases. What was the course of the papilledema? Is the cause related to some disturbance in the electrolytes?

DR. H. A. SHENKIN: What was the cause for the patient's increase in intracranial pressure?

DR. S. WOLFE: Thirteen per cent of the cases in the literature showed papilledema. In the case under discussion, the papilledema decreased with treatment.

Abstracts from Current Literature

EDITED BY BERNARD J. ALPERS

Physiology and Biochemistry

BEHAVIOR OF CHIMPANZEE-AVIRULENT POLIOMYELITIS VIRUSES IN EXPERIMENTALLY INFECTED HUMAN VOLUNTEERS. ALBERT B. SABIN, Am. J. M. Sc. **230**:1, 1955.

Strains of three types of poliomyelitis virus, experimentally segregated in monkey kidney tissue culture and avirulent for monkeys by intracerebral and extraneural routes, were administered to 30 human volunteers who had no antibody for the poliomyelitis viruses. Twenty-six men received Types 1, 2, or 3 virus in doses from 0.001 to 1 cc. by mouth. The others who were without antibody for all three types received Type 3 virus intramuscularly. Only when large doses were given by mouth did the virus multiply in the throat, but even the smallest amounts initiated an immunogenic alimentary infection in all subjects. No viremia was found in any of the volunteers, and there was no evidence of even minor illness. The amounts of Type 3 virus which produced infection after ingestion failed to do so after intramuscular injection except in one man, in whom the virus localized in the lower alimentary tract. The antibody response was of a higher order in subjects with extensive viral multiplication in the throat. No harmful mutants were found after multiplication in the alimentary tract.

BERLIN, New York.

THE EFFECT OF HEPARIN ON THE CEREBRAL BLOOD FLOW OF ELDERLY STATE HOSPITAL PATIENTS. R. W. TALLEY, Am. J. M. Sc. **230**:61, 1955.

The cerebral blood flow was measured by the nitrous oxide technique of Kety and Schmidt in 11 patients past the age of 65 who had senile brain degeneration and/or a cerebrovascular lesion. Measurements were made in the fasting state and then repeated after the patient had received 200 mg. of heparin intravenously. Control studies were made on six patients under the age of 40. Although the cerebral blood flow and cerebral oxygen utilization were decreased and the cerebral vascular resistance was increased in the older subjects, there was no significant change in any of these values in either group.

BERLIN, New York.

DETERMINATION OF CEREBROSIDES. N. S. RADIN, F. B. LAVIN, and J. R. BROWN, J. Biol. Chem. **217**:789, 1955.

Cerebrosides are determined colorimetrically by removing interfering lipids by a column packed with Florisil and mixed ion exchange resins. The crude cerebrosides are determined by a modification of the anthrone method, in which the lipid is rendered soluble by preliminary heating with phosphoric acid. An inverse phase-partition column is described in which polystyrene spherules are used to immobilize the organic nonpolar phase.

PAGE, Cleveland.

ANATOMICAL AND ELECTRICAL STUDY OF CORNU AMMONIS IN 4 EPILEPTIC PATIENTS SUBJECTED TO HEMISPHERECTOMY. P. PASSOUANT, C. GROS, L. VAN BOGAERT, and G. CADILHAC, Rev. neurol. **92**:96, 1955.

Four subjects, from 9 to 28 years of age, who had been subjected to hemispherectomy were studied relevant to the electrical activity of the cornu ammonis. All four patients had seizures and mental retardation, and three had hemiplegia. In those subjects who had anatomical changes in the cornu ammonis, in the form of degeneration of the neurons and glial proliferation, the spontaneous electrical activity was characterized by continuous slow waves, and, where the sclerotic changes were most marked, the diphasic slow waves were often separated by periods of electrical silence. In the case in which the cornu ammonis was histologically normal, the subject exhibited high-voltage spikes in an otherwise normal record. In the cases of severe atrophic cornu ammonis the threshold for evoking an electrical response was elevated, and 5-6 volts of

stimulations evoked only a brief period of short spikes. In the case of a normal hippocampus, the threshold was low, the discharge following stimulation was prolonged, and numerous slow spikes appeared rhythmically.

BERLIN, New York.

ACETYLCHOLINE AND THE CEREBRAL CORTEX. J. E. DESMEDT and A. LA GRULTA, Rev. neurol. **93**:478, 1955.

The role of butyrocholine esterase, which is associated with neuroglia, was investigated in an *encéphale isolé* preparation of a cat without using anesthesia or curarization. Using substances selectively which inactivated butyrocholinesterase, the authors demonstrated that inhibition of butyrocholinesterase accelerates and desynchronizes the electrocorticogram and causes an arousal reaction. This suggests that the neuroglia are capable of participating in the control of humoral agents bathing the neurons.

BERLIN, New York.

Meninges and Blood Vessels

COMBINED SUPRA- AND INFRACLINOID ANEURYSMS OF THE INTERNAL CAROTID ARTERY. J. C. WHITE and R. D. ADAMS, J. Neurosurg. **12**:450, 1955.

White and Adams report the presence of an irregular fusiform aneurysm arising at the bifurcation of the internal carotid and ophthalmic arteries in a 16-year-old boy who had a history of gradual loss of vision in the left eye of one year's duration, left temporal headaches, numbness of the left side of the face, double vision, and loss of taste over the left side of the tongue. Neurological examination revealed a dilated left pupil which did not react to light, optic atrophy of the left disc with a visual acuity of 5/200 and an eccentric scotoma of the left eye, complete paralysis of all ocular movements of the left eye, and loss of taste over the left half of the tongue. A left percutaneous arteriogram demonstrated a huge aneurysm, extending from a dilated foramen lacerum throughout the length of the cavernous sinus and then upward, behind and above the anterior clinoid process. The aneurysm was occluded by direct surgical approach, and the patient improved except for almost complete blindness of the left eye.

This case was of interest because of the unusual type of aneurysm which was encountered, namely, an irregular fusiform expansion which extended from the foramen lacerum nearly to the end of the carotid artery, the widest part being in the intracavernous portion. The authors believe that this aneurysm was a congenital arterial malformation, since it was associated with two small nevi on the left upper lip and temple. The aneurysm gradually expanded, with the supraclinoid portion compressing the optic nerve and the infraclinoid portion the fourth, fifth, and sixth cranial nerves, presumably injuring the greater superficial petrosal branch of the facial nerve as well. In addition, the unique feature of the loss of taste could be attributed to an accessory taste pathway carying gustatory fibers from the lingual to the facial nerve, the usual route, via the chorda tympani, being absent. The greater superficial petrosal nerve was injured by the aneurysm as it coursed medially beneath the Gasserian ganglion.

MANDEL, Philadelphia.

TUBERCULOUS MENINGITIS OF ACUTE ONSET. K. B. TAYLOR, H. V. SMITH, and R. L. VOLLUM, J. Neurol. Neurosurg. & Psychiat. **18**:165, 1955.

Tuberculous meningitis is usually characterized by insidious onset, but the authors report eight cases of tuberculous meningitis with acute onset in a series of 200 unselected cases. The syndrome was characterized by acute abrupt onset, with an unusually high cell count in the spinal fluid, at least 500 white cells being found. In three cases the cells at the time of the first lumbar puncture were virtually all lymphocytes, but in the other four cases there was a considerable number of polymorphonuclear cells, 82% being found in one instance. The prognosis is good in the acute cases with adequate chemotherapy.

The authors suggest that the pathogenesis in acute cases is the sudden rupture of a comparatively large caseous focus, or "Rich's focus," with release of its contents into the spinal fluid. These contents are impregnated with tubercles and contain tubercle bacilli, which are in themselves antigenic. The result of this rupture is a brisk intrathecal tuberculin reaction, which subsides in a few days; but the tubercle bacilli then cause the reaction which is found in acute tuberculous meningitis. To support this tuberculin theory, the authors report a case in which death occurred during the phase of acute tuberculin reaction; examination of the brain revealed no

exudate or gross abnormalities. The microscopic examination revealed a cellular exudate over the hemisphere similar to that observed in experimental animals which were sensitized to tuberculin and then given intrathecal injections of tuberculin.

The authors conclude that the spinal fluid changes in tuberculous meningitis are the expression of an antibody-antigen response of intrathecal tuberculin reactions secondary to rupture of a caseous focus.

MANDEL, Philadelphia.

Diseases of the Brain

THE NEUROLOGICAL MANIFESTATIONS OF CAT SCRATCH DISEASE. L. WEINSTEIN and R. H. MEADE, Am. J. M. Sc. **229**:500, 1955.

A 17-year-old white girl, four days after the most recent of numerous cat scratches, developed a febrile illness with meningoencephalomyelitic signs. She had a stiff neck, lethargy, weakness of the legs, decrease of all sensory function up to the hips, and spasticity of both lower extremities. There were pleocytosis and increased protein and sugar in the spinal fluid. The disabilities gradually diminished after 16 weeks, and the patient was able to walk unassisted and had only minor sensory defects.

BERLIN, New York.

PROGRESSIVE FAMILIAL MYOCLONIC EPILEPSY. D. G. F. HARRIMAN and J. H. D. MILLAR, Brain **78**:325, 1955.

Harriman and Millar report eight cases of the syndrome of progressive familial myoclonic epilepsy in three separate families. In each family, all cases occurred in the same generation and there was no case in the preceding generation. The families were unrelated. The condition follows the pattern of single-gene recessive inheritance in man. There was no history of epilepsy in any of the families, although in one instance the father and one brother had Parkinsonism. The age of onset was 14 years in the first family, between 7 and 14 years in the second family, and between 19 and 27 years in the third family. The onset in two families was with myoclonus and grand mal seizures, whereas in the third family the myoclonus did not appear until the terminal state.

The myoclonus was characterized by sudden jerking movements of the individual muscles, which produced displacement of the limbs and trunk and was increased by active and passive movements, changes in posture, emotion, and photic stimulation. Usually the myoclonus disappeared in sleep, although in two cases it continued, though diminished. The muscles of articulation were affected by the myoclonus, and the resulting dysarthria was the most striking feature in some cases. The terminal stage was manifested by progressive dementia, ataxia, incontinence, and a bedridden state, the patient assuming an attitude of flexion of the legs. All patients had bilaterally synchronous sharp waves in the electroencephalogram with the clinical myoclonus.

An autopsy was performed in one case; and microscopic examination of the frontal, motor, temporal, and occipital cortex revealed the presence of numerous intra- and extracellular amyloid bodies, similar to those described by Lafora, but the bodies had a predilection for the substantia nigra and dentate nucleus. They were noted in the posterior horns of the spinal cord and the heart and liver as well. The distribution of the amyloid bodies was most marked throughout Layers II to IV of the cortex. The bodies were basophilic with all stains used and usually had a dark-staining core bound by pale- and dark-staining rings. Occasionally three to five bodies were found within the cytoplasm of one nerve cell body. Another abnormality was the presence of a large number of nerve cells containing lipofuchsin pigment, the number being greater than usual at the stated age. By histochemical methods, the material was found to belong to the group of acid mucopolysaccharides, suggesting that the underlying disorder in cases of this nature is a disturbance of intracellular metabolism. Although the substance resembled amyloid to a certain degree, histochemically it was not deposited in the interstitial tissues of blood vessel walls, which were normal in this case.

Amyloid inclusion bodies have been found in conditions other than myoclonus, some of the more important ones being amaurotic family idiocy, postencephalic Parkinsonism, and Friedreich's ataxia. Whatever the pathogenesis, the common factor appears to be brain stem involvement, with involvement in addition of the dentate nucleus and its efferent connections.

MANDEL, Philadelphia.

CHRONIC EPIDURAL ABSCESS AND CONDENSING OTEOMYELITIS OF THE FRONTAL BONE. C. A. WHITTEN and J. B. MOYAR, J. Neurosurg. **12**:516, 1955.

Chronic epidural abscess with hyperplastic bone changes extending over a period of years without outward manifestations is not encountered frequently. Whitten and Moyar report the case of a 35-year-old woman who was admitted to the hospital with the complaints of severe headache, nausea and vomiting, and double vision. She also noted blindness in the right visual field with unsteady, staggering gait. Her past history revealed pansinusitis 21 years before admission with roentgenographic evidence of osteomyelitis of the right frontal bone. The bone was curetted, and a small amount of purulent material was removed beneath the necrotic bone. One year later x-rays showed chronic osteomyelitis involving the left frontal bone and orbital plates. Drainage persisted throughout the following five years but finally ceased after débridement of the necrotic tissue and bone. She was asymptomatic throughout the following 12 years, when symptoms of headache, nausea, and vomiting appeared. Neurological examination revealed bilateral papilledema and weakness of both lateral rectus muscles, and visual field examination showed right incongruous homonymous hemianopsia. Roentgenograms of the skull revealed an extensive sclerotic reaction along the medial aspect of the left frontal bone. At operation, a large amount of extremely thickened eburnated bone was removed, with 5 cc. of purulent material beneath this thickened bone. Culture of this material revealed nonhemolytic Staphylococcus aureus. Her headaches, vomiting, and double vision subsided.

This case demonstrates the fact that an infection of low virulence in the epidural space can exist for 12 years without outward signs of its presence. This confirms the impression that cranioplasty following contaminated or infected wounds of the skull, even though done a year or more following the original removal of bone, is not without danger. MANDEL, Philadelphia.

CERTAIN FALSE LOCALIZING SIGNS OF INTRACRANIAL TUMOR. H. W. DODGE JR., E. C. CLARK, H. P. WAGENER, and A. P. HUSTEAD, Proc. Staff Meet. Mayo Clin. **30**:453, 1955.

There are many causes of false localizing signs of intracranial neoplasms, the most important of which is increased intracranial pressure. If the signs found by the neurological examination are manifested before the general symptoms and signs of increased intracranial pressure occur, they have localizing value. If the general signs occur first or if the patient is seen after the signs of increased intracranial pressure occur, then further studies, such as ventriculography, must be used for differentiation. Localizing signs that may occur as false signs in such instances include those referable to the cranial nerves, cerebellum, motor system, and cerebrum.

The authors report the case of a 13-year-old white girl who had a history of headaches, vertigo, and double vision. She had an episode of unconsciousness, following which she had difficulty in maintaining her balance. Neurological examination revealed cracked-pot resonance of the skull, horizontal nystagmus to the left, right lateral rectus paresis, diminished right corneal reflex, and right peripheral facial palsy. Weakness of the soft palate and pharynx on the right was noted; she had a tendency to fall to the right, and adiadokokinesis was more marked on the right. Bilateral papilledema was present, measuring 4 D., and perimetric determination of the visual fields revealed a midline right homonymous hemianopsia. From the examination, the cranial nerve signs with dysmetria and ataxia were incompatible with the right homonymous hemianopsia. An electroencephalogram was suggestive of a left supratentorial lesion. In order to differentiate the false from the true localizing signs, a ventriculogram was performed, which revealed a large cystic lesion in the parietal region. At operation, an astrocytoma was removed from the left parietal lobe.

As demonstrated in this case, involvement of the cranial nerves controlling extraocular muscles can occur in association with supratentorial tumors of the brain. An abducens palsy may occur rapidly, owing to sudden compression or displacement of the brain stem. The oculomotor nerve was compressed by herniation of the uncus, probably accounting for this distant false localizing sign. Notching of the crus cerebri by the free margin of the tentorium of the cerebellum may cause false pyramidal tract signs. Unconsciousness may occur from downward displacement and compression of the posterior fossa. Mental disturbances frequently occur as the result of internal hydrocephalus, and not as a frontal lobe sign.

The importance of utilizing ventriculography in the presence of increased intracranial pressure with focal signs in order to eliminate false localization of the neoplasm is emphasized.

MANDEL, Philadelphia.

CONGENITAL HEREDITARY VERTICAL NYSTAGMUS, W. I. FORSYTHE, J. Neurol. Neurosurg. & Psychiat. **18**:196, 1955.

Congenital nystagmus varies considerably in extent, direction, and rapidity, but it is most frequently bilateral, the movements being pendular in type and horizontal in direction. Several pedigrees of congenital nystagmus of the horizontal type have previously been reported, but congenital nystagmus of the vertical type is rare.

Forsythe reports five cases of congenital vertical nystagmus in a family of Italian extraction, which involved three generations. Three male and two female members were examined in this series, the ages varying from 15 months to 67 years. In each instance the nystagmus was binocular, synchronous, and vertical in type, and the movements were pendular. In three patients, head movements were observed, but they were not in the same plane as the nystagmus and their rate was slower. The head movements diminished during fixation and increased while gazing abstractedly. Fixation and alteration of the visual axes had no effect on the nystagmus. The actual site of the lesion in congenital nystagmus is not known, although numerous hypotheses, which include weakness of the ocular muscles, anomalies of the vestibular tract and their connections with the labyrinth, and involvement of Deiters' nucleus, have been suggested.

This condition probably is best listed in Duke-Elder's classification of congenital nystagmus, since this is an ambisexual, irregularly dominant form with frequently associated head movements.

MANDEL, Philadelphia.

CHORDOMA OF THE CLIVUS: REPORT OF A CASE. S. MINGRINO, Acta neurol. **10**:439, 1955.

Approximately 130 intracranial chordomas have been reported to date; they may originate from notochordal remnants anywhere along the midline of the base of the skull and may simulate clinically various types of middle and posterior fossa tumors.

The case reported was that of a 15-year-old youth with weakness of the left abducens nerve of two years' duration. For six months prior to admission, headaches, equilibratory disturbances, hearing loss, dysphagia, and dysphonia had developed. Examination revealed clouding of the sensorium, with urinary and fecal incontinence, bilateral papilledema, a left hemisensory defect over the face, left facial weakness of peripheral type, and bilateral hearing loss. Point-to-point tests were poorly performed throughout. There was slight weakness of the right lower extremity, with a right Babinski sign.

Skull films were negative. Following angiography, a posterior-fossa exploration revealed a large encapsulated, yellowish tumor containing gelatinous material and extending from the clivus into both cerebellopontile angles, the left being primarily invaded. Death occurred a few days after operation. Microscopically, the tumor showed a cellular pattern typical of a chordoma.

NORSA, New York.

NEUROLOGICAL COMPLICATIONS OF DIABETUS MELLITUS. P. DAZZI, Riv. pat. nerv. **76**:557, 1955.

Dazzi reviews the problem of the neurological complications of diabetes in respect to peripheral neuropathy, radiculomyelopathy, encephalopathy, and cranial neuropathy. Among the myelopathies, involvement of the anterior horn cells, the dorsal columns, and/or the lateral columns has been reported clinically and pathologically.

Involvement of the extraocular movements and of the seventh, eighth, and fifth nerves has been described; it has been attributed either to brain stem thromboses and hemorrhages or to vascular insufficiency secondary to arteriosclerotic plaques.

NORSA, New York.

Diseases of the Spinal Cord

ACUTE NECROTIC MYELOPATHY. H. L. HOFFMAN, Brain **78**:377, 1955.

Acute necrotic myelopathy consists of the rapid softening or necrosis of the spinal cord, which is manifested clinically by a flaccid paralysis, with a sensory loss from the thoracic level or higher to the lower extremities and complete loss of sphincter control. Death may occur in the acute stage if the bulbar centers are involved, or the patient may succumb to a urinary tract infection or to the effects of complicating decubitus ulcers. During the survival period, no

recovery of function occurs below the upper level of the lesion. Spinal fluid changes are inconstant, and studies may reveal occasional white cells with a normal or slightly elevated protein level.

Hoffman reports three cases of acute necrotic myelopathy with autopsy findings and two other cases in which the patients survived the disease. Gross examination of the spinal cord in each case revealed extensive areas of softening throughout all levels of the involved cord, a small area of suppuration being associated with the softened area in one case. The white matter appeared to be more severely involved than the gray matter. Areas of demyelination were noted in the posterior columns and the spinothalamic and spinocerebellar tracts. The lateral columns were involved sporadically, and the gray matter was shrunken in many of the involved segments. The blood vessels were normal throughout all levels, there being no evidence of thrombosis or thickening of the intima or walls, such as was noted by other observers. Hoffman believes that vascular hyperplasia is not an important feature of this disease and is not the cause of the necrosis, but the necrosis and blood vessel changes which others have found are simultaneous responses to some toxic or infectious agent.

Microscopic examination of the cord revealed some acute areas with loss of cells and older areas with necrosis and gitter-cell infiltration. No sclerosis or thrombosis was present in the blood vessels. In the third case a lymphocytic and polymorphounclear response was present, which was thought to be secondary to the necrosis.

There was a definite history of an infective process preceding the onset of the necrotic myelopathy in a number of instances. Hoffman believes that bacterial infections are the most likely etiological factors in acute necrotic myelopathy, whereas infections due to non-neurotropic viruses are associated rather with acute disseminated encephalomyelitis. Corticotropin should not be used, for in one case it was thought to have been responsible for dissemination of an abscess.

MANDEL, Philadelphia.

ABSCESS FORMATION IN THE SPINAL CORD. E. B. KEENER, Brain **78**:394, 1955.

From a histologic standpoint, intramedullary spinal cord tumors are divided into two groups. The first group comprises about 25% of the cases and consists of small multiple focal areas of abscess formation, and the second group, of 75%, comprises the large abscesses, which usually extend for several cord segments.

Keener reports a case of an intramedullary cord abscess and two brain abscesses in a 53-year-old man who had an episode of bronchitis and fever five weeks before admission to the hospital but remained bedridden until four and a half weeks later, when he noted pain in the chest at the level of the right nipple and weakness of both legs. Neurological examination revealed the patient to be febrile; the right pupil was smaller than the left; the right corner of the mouth drooped while at rest, and a flaccid paraplegia of the legs with absence of deep reflexes was noted. Pain and temperature sense were diminished bilaterally below the inguinal ligament. Vibratory sensation was absent over the left lower limb and diminished over the right. The spinal fluid showed 19 white cells and 240 red blood cells per cubic millimeter and 65 mg. of protein per 100 cc. During the period of observation paralysis of the intercostal muscles and paralysis of both arms developed. He was placed in a respirator, and within two weeks bilateral facial weakness, dysphagia, and dysarthria developed. The sensory level ascended to the fourth cervical level, and a bilateral Babinski sign became evident. He died within five weeks after his admission to the hospital, after an unsuccessful response to antibiotics, consisting of penicillin and chloramphenicol.

Gross examination of the brain revealed a multilocular abscess in the lower part of the left precentral gyrus, involving part of the motor cortex and white matter. The abscess itself consisted of a well-encapsulated lateral locule and two less well-demarcated medial locules. A second abscess was found in the upper medial aspect of the right occipital lobe. Transverse sections of the brain stem and spinal cord showed an oval cylindrical lesion, 3 mm. in diameter, extending from the lower third of the medulla to the third lumbar segment. In the medulla, the abscess was at the base of the posterior median fissure to the right of the midline, and in the spinal cord it involved the posterior columns with extension into the posterior gray matter and the anterior columns. A smear of the pus from the left cerebral hemisphere contained chains of Gram-positive cocci.

Microscopic examination showed that the lateral abscess was encapsulated but the medial loculi were not. The occipital-lobe abscess was encapsulated and had a slight proliferative zone

of astrocytes about it. The necrotic centers consisted typically of lymphocytes, polymorphounclear neutrophiles, gitter cells, and plasma cells. A definite connective-tissue capsule was seen only in the rostral portion of the abscess in the lower portions of the medulla, but throughout the abscess a fine connective-tissue network with capillaries was present. Glial formation was not marked about the abscess. There was a striking absence of polymorphonuclear cells in the spinal cord abscess, the necrotic center here consisting of plasma cells and microglial cells. No organisms were found in this abscess.

This case was unusual in that the abscess was of extensive length and was confined to the region of the posterior columns. The absence of the capsule throughout the spinal cord indicates that the abscess was of more recent origin here than in the medulla, where a definite capsule was present. The absence of polymorphounclear cells in the necrotic center of the cord was also remarkable, as compared with the large number of these cells in the brain abscess.

Keener postulates that the abscess originated in the medulla and the pus, under increased pressure, extended caudally by separation rather than by destruction of the posterior longitudinal pathways. Wedge-shaped necrotic areas of necrosis were also present in the spinal cord, corresponding to the pattern of venous drainage of the cord.

MANDEL, Philadelphia.

EARLY DIAGNOSIS OF COMPRESSION OF THE SPINAL CORD BY NEOPLASMS. G. F. ROWBOTHAM, Lancet **2**:1220, 1955.

Rowbotham reviews 80 cases of compression of the spinal cord by neoplasm. In this series of 80 cases there were 46 extramedullary neoplasms arising from one of the tissues of the spinal cord. In reviewing his cases, the author concludes that in malignant constriction of the spinal cord by silent primary neoplasm the neurological signs are much the same as those caused by the compression from a primary benign neoplasm. In cases of cancer, however, the patient may be fully paralyzed within a few days of the first signs of weakness, whereas in cases of benign neoplasm the paralysis develops slowly, over months or even years. It is impossible to identify the origin of spinal cord compression by the first symptom. Neoplasms that are surgically curable nearly always progress slowly, and it is often possible to make a diagnosis on clinical evidence alone before irreversible damage has been done to the spinal cord. Rowbotham emphasizes that a negative Queckenstedt test by no means excludes spinal compression. In the 20 cases of compression of the spinal cord by secondary deposits the primary growths were situated as follows: bronchus, 7; prostate, 6; breast, 5; kidney, 1, and stomach 1.

YASKIN, Camden, N. J.

Treatment, Neurosurgery

ON SUBARACHNOID BLEEDING—AN APPRAISAL OF TREATMENT. J. W. MAGLADERY, J. Neurosurg. **12**:437, 1955.

Magladery reviewed 235 unselected cases of subarachnoid hemorrhage from 1947 to 1954 and found an over-all mortality rate of 50%. Death was greatest in cases in which hemorrhage occurred in older patients, hypertensive patients, or patients admitted in coma. Most of the deaths occurred within 24 hours after admission to the hospital; thereafter, of the patients handled conservatively, only 20% died. After seven days, the prognosis became statistically good, and 88% survived. Those patients who were managed conservatively and lived longer than three weeks had an infinitely lower prospect of death.

In regard to the question of angiography during subarachnoid hemorrhage, 90 of the 235 were subjected to arteriography. Of the 90 angiograms, 48 (53%) revealed no evidence of arterial aneurysm, angioma, or arteriovenous malformation. Furthermore, the incidence of positive arteriograms was lowest when the procedure was performed within the first seven days. In 10 patients angiography was found to accompany or precede immediately rapid deterioration, culminating in death. Five of these patients were critically ill, and Magladery states that death may have been coincidental; but in the remaining five cases there is adequate information available to suggest that the procedure could justifiably be blamed. In all instances surgery, when it was undertaken, was carried out soon after arteriography; the first week was crucial in terms of survival, for only one of 12 patients survived who were exposed to surgery. Of those having angiography between the first and third weeks, few died when treated merely symptomatically. With surgical intervention the mortality rate was about 50%. After the third week, among those having angiograms there were no deaths, regardless of the form of therapy.

Magladery therefore concludes from his present series that definitive surgery in the immediate treatment of spontaneous subarachnoid hemorrhage does not offer any improvement over the conservative approach.

MANDEL, Philadelphia.

RESULTS OF DIRECT ATTACK ON INTRACRANIAL ANEURYSM. S. N. ROWE, J. F. GRUNNAGLE, A. SUSEN, and J. S. DAVIS, J. Neurosurg. **12**:475, 1955.

The authors state that in the absence of cranial trauma and hypertension, ruptured intracranial aneurysm is the most frequent cause of subarachnoid hemorrhage. In a series of 81 patients 24 to 60 years of age with verified intracranial aneurysms, 22 were treated conservatively, 25 had ligations of one carotid artery in the neck, and 34 were treated by direct approach of the aneurysm through craniotomy. When subarachnoid hemorrhage was present, surgery was performed 5 to 43 days later, with an average of 18 days. This practice is at variance with other reports, which suggest operation during the quiescent period between hemorrhages, with at least a three-week interval following the last hemorrhage. The authors believe that the loss of patients from recurrent hemorrhage during the second and third week might be greater than the increased operative mortality. The operative procedures included clipping the neck of the aneurysm, intracranial trapping, proximal clipping, and packing with muscle.

The authors report seven deaths in this group, or a mortality of over 20%. Technical problems were known to be the principal cause of death in two instances, whereas postoperative complications, such as cerebral edema and pulmonary edema, resulted in death in four other cases. Although other reports reveal a lower mortality when surgery is performed during the quiescent period, the authors state that their mortality is lessening as a result of the use of hypotension during surgery, employment of Olivecrona clips, and control of intracranial edema during and after operation. Therefore, it is felt that with improvements in operative technique, intracranial operation on aneurysms will become less hazardous and will be the treatment of choice.

MANDEL, Philadelphia.

STILBAMIDINE ISETHIONATE THERAPY OF TIC DOULOUREUX. B. WOODHALL and G. L. ODOM, J. Neurosurg. **12**:495, 1955.

The authors report the use of an intravenous solution containing 0.15 gm. of stilbamidine isethionate dissolved in 150 cc. of 5% dextrose and distilled water for the treatment of severe pain in tic douloureux. The course of therapy consisted of 10 daily injections, for a total of 1.5 gm. Fifteen of the patients were men and 26 were women, with their ages varying from 32 to 86 years. The patients developed a chemical neuropathy from the stilbamidine which relieved the pain and was associated with sensory changes over the trigeminal and upper cervical dermatomes. Of the 41 patients, 36 obtained relief from their pain for a period ranging from nine months to two years. In a small number of cases, unpredictable formication and paresthesias occurred, which may decrease the therapeutic efficacy of this drug. Nevertheless, this drug may be a valuable adjunct to the care of tic douloureux, and the beneficial results should warrant further study of stilbamidine for intravenous and oral use.

MANDEL, Philadelphia.

DIFFERENTIAL DORSAL ROOT SECTION IN THE TREATMENT OF BILATERAL TRIGEMINAL NEURALGIA. B. STOOKEY, J. Neurosurg. **12**:501, 1955.

Bilateral trigeminal neuralgia occurring with or appearing after unilateral trigeminal neuralgia imposes a formidable problem of treatment. The consequences of bilateral loss of sensation and the inherent threat of damage to the motor innervation of the muscles of mastication have made the surgeons reluctant to operate.

Stookey reports four cases of bilateral trigeminal neuralgia which was treated by bilateral selective dorsal root section of the trigeminal nerve by the transtemporal approach. In each instance, the patient had had a previous episode of trigeminal neuralgia of the opposite side which had been treated by similar selective dorsal root section. Prior to the second operation, conservative treatment, consisting of alcohol injections and high doses of cyanocobalamin had failed to alleviate the pain. Following surgery, each patient experienced freedom from pain and had no weakness of the muscles of mastication.

Stookey advocates the transtemporal approach for root section because of the ease with which the operation may be performed and the lack of complications through selective root section.

He does not recommend tractotomy, since the cerebellar pathways and fibers to the masticatory muscles may be involved in high sections and the ophthalmic fibers in the descending trigeminal tract may be injured in the more caudal tractotomy.

MANDEL, Philadelphia.

Muscular System

TWO OBSERVATIONS ON ACUTE GENERALIZED (WAGNER-HEPP) POLIOMYELITIS. M. A. RADERMECKER and L. VAN BOGAERT, Rev. neurol. **92**:182, 1955.

The authors report two cases of acute generalized poliomyelitis in an 8- and a 13-year-old child, in both following mild acute infections. The symptoms were characterized by pain; fatigability, and progressive edema of the lower extremities, abdominal wall, and the upper extremities, and even of the face. The deep reflexes were reduced, although muscle tonus was increased. After a few weeks, there developed myocardial changes with a mitral murmur and gallop rhythm. There was marked tenderness of all the muscles and involvement of the ocular muscles and of the muscles of deglutition. Death occurred in four to seven months. The muscles were edematous and had the color of fish muscle; they showed marked edema, fragmentation of the fibers, and diffuse, as well as perivascular, infiltration with plasma cells. The skin also showed evidence of atrophy, edema, and cellular infiltration.

BERLIN, New York.

Encephalography, Ventriculography and Roentgenography

TOWARD SAFER ANGIOGRAPHY. C. B. SEDZIMIR, J. Neurosurg. **12**:460, 1955.

Sedzimir reports a series of 273 carotid angiograms on 169 patients without death or complications. In this group of patients, general anesthesia with gas and oxygen was used in order to relieve the apprehension of the patient and to reduce the pain caused by the contrast medium. This was thought to reduce any generalized vasospasm, thus preventing complications due to procedure. Arteriodone, in a concentration of 42.5%, was found to be the most satisfactory contrast medium when used in these anesthetized patients. Sedzimir also found that less complications were encountered by repeated carotid injections with a sharp 18-gauge needle than by permitting the needle to remain in the lumen of the artery and injecting saline or citrate mixture to keep the needle open. A 6-in. length of polyethylene tubing was also found to lessen the force of the injection and minimize the risk of air embolism.

The ages of the patients in the series varied from 1 to 65 years. There were 23 cases of subarachnoid hemorrhage the etiology of which was not determined by angiography and 27 cases of berry aneurysm investigated after one or more hemorrhagic incidents. Eight aneurysms which had bled and eight aneurysms and arteriovenous aneurysms which had not ruptured were found by this study. Angiography was performed on the 10th day in cases of subarachnoid bleeding; the patient's progress was satisfactory and no complications were encountered. Sedzimir believes that arteriography should not be performed in cases in the 50- to 70-year age group in which a definite diagnosis of cerebral thrombosis can be made. In younger patients, when there is doubt as to the diagnosis, angiography is justified. Five cases of thrombosis of the internal carotid artery were found in this series. In regard to tumors, angiography was found to be very valuable, particularly with supratentorial neoplasms, and no fatalities were found.

MANDEL, Philadelphia.

News and Comment

ANNOUNCEMENTS

Course in Neuromuscular Diseases of Children, Cook County Graduate School of Medicine.—The Cook County Graduate School of Medicine announces a two-week intensive course in Neuromuscular Diseases of Children, with special emphasis on cerebral palsy, to be given by Dr. Meyer A. Perlstein for the two-week period of June 18 to 29. This is an intensive, didactic, and clinical course designed for pediatricians, orthopedists, neurologists, and physiatrists interested in the care and treatment of children with neuromuscular handicaps. Emphasis will be placed on the practical clinical aspects of treatment and rehabilitation procedures. The course will include several field trips to demonstration clinics and treatment centers. The fee for the course, which is $225, includes the cost of luncheons as well as the expense of travels, meals, and accommodations on the various trips. Registration in the course is limited. For further information, write to John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 S. Wood St., Chicago.

First International Congress of Human Genetics.—The First International Congress of Human Genetics will be held in Copenhagen, Denmark, Aug. 1-6, 1956. This Congress is planned to cover all genetic aspects of normal and pathological characters in man. Any person interested in the subject of human genetics, and especially of medical genetics, is invited to take part in the Congress.

A provisional program and further information will be sent on request to the Secretariat of the First International Congress of Human Genetics, The University Institute for Human Genetics, 14, Tagensvej, Copenhagen, N., Denmark.

Books

Encyclopédie médico-chirurgicale—Psychiatrie. Three Volumes. Edited under the direction of Dr. Henri Ey, with the cooperation of psychiatrists of *l'Evolution Psychiâtrique*; M. Coumétou, secretary-general of the edition, Encyclopédie médico-chirurgicale, 18 rue Séguier, Paris VI, 1955.

Under the leadership of Henri Ey, French psychiatrists have offered to their colleagues of two continents an excellent "Encyclopedia of Psychiatry." The three volumes of the "Encyclopedia" are perhaps a little bulky, but they are easily manipulated; they are artistically, if not sumptuously, presented, and they should satisfy the expectations of seasoned book lovers. They are typical of French fine editions.

The contents have been written by high-grade contributors. They include the whole of fundamental psychiatry, plus all aspects of immediate and remote interests in the connected fields, for example, exotic sociopsychology, expert reports in canon law, and existential analysis.

Each and every chapter is dealt with exhaustively and expresses all opinions on a given subject as of today. International bibliographies point to the universal sources of information.

Serious contributors from all schools are freely accepted, while nationalisms are so little felt that all three volumes could have been written as well in any other language. However, this treatise is written in French—even so for English-speaking readers—because the secular clarity of the old diplomatic idiom is frequently helpful along the obscure and nebulous pathways of psychiatry.

It is not an easy task to translate with full accuracy the precise meaning of what psychoanalysts wish to convey, and yet doctrinal and critical articles describing Freudian and Jungian concepts become clear and limpid under the pen of French psychiatrists.

It has always been felt by this reviewer that the proper wording of a paper unfolding psychiatric doctrine or describing mental mechanisms was somewhat of a challenge to convey precise and adequate meaning into the mind of the recipient. In the hands of clever writers the French language becomes a precious instrument whereby that which is intricate, heavy, and complex in a new theory or discipline becomes fined down and ventilated.

Many chapters are so intimately linked with the author's personality and tendencies that a signature becomes a preposterous evidence; for example, certain far-reaching statements and syntheses are obviously Ey's productions.

This is neither the place nor the time to discuss each of the three volumes of the "Encyclopedia." Even if it were eminently profitable, it does not seem possible to do so within the narrow scope of a mere presentation column. However, one should outline the praiseworthy care with which all chapters of psychiatry have been rewritten and adapted to recent acquisitions. It is as if all contributors to this gigantic work had joined in their endeavor to set the psychopathological kaleidoscope of human beings in its holistic perspective. They lay stress at times upon the atomistic theory of Clérambault via Ey's organodynamic doctrine and neo-Jacksonianism, at other times, upon the Gestalt psychology and many other analogous or opposite theories; they finally discuss at length the powerful and ever-present solicitations of the unconscious, individual and collective.

The separate booklet entitled "World Psychiatry" should render appreciable services to French and other psychiatrists who are not familiar with foreign disciplines and conceptions. One will observe, on the one hand, that psychoanalysis and lobotomy are taboo in U. S. S. R. and, on the other hand, that the U. S. A. have become extremely psychiatry-conscious.

The three volumes of this "Encyclopedia" will be read with interest by psychiatrists of the whole world who have the advantage of being conversant in French. They should be glanced through by those who have some knowledge of French. Because of their importance they will be found in the libraries of institutes and hospitals where French is hardly known. Nonspecialized physicians will find in their pages a cultural gold mine which should delight their leisure hours. Psychologists, scholarly nurses, and educators are certain to augment by their perusal their knowledge of the human person.

Very likely this formidable *Summa psychiatrica* would not have been born yet without the dynamic incentive of its director, whose achievement has already been acknowledged by all European psychiatrists.

Aphasia Therapeutics. By Mary C. Longerich, Ph.D., and Jean Bordeaux, Ph.D. Price, $3.75. Pp. 185. The Macmillan Company, 60 Fifth Ave., New York 11, 1954.

This book gives to the practitioner a well-organized guide to treatment in Chapters V through VII. The authors summarize their point of view in Chapter IX by saying: "In brief, the psychological goal in the therapeutic treatment of an aphasia victim should be to aid him in recovering his integrity as a well-functioning individual. If treated as an infant, the prospects for recovery are poor indeed. But when therapy improves both the speech and language loss, and induces the sufferer to make genuine efforts to use all his physical capacities (regardless of how much these may have been reduced by cerebral insults), the possibilities for recovery are enhanced and progress toward that goal is speeded up immeasurably." This is excellent, but the book strikes one as a rather amateur effort, written with a chip on the shoulder. No doubt the great clinical experience of these authors has given them evidence to doubt the ability of physician, nurse, and family to help aphasic patients. Probably they have seen many patients mistreated and have good reasons for writing vigorously in defense of the aphasic patient. But all this does not give them justification for making many inaccurate, exaggerated, and obviously emotional statements.

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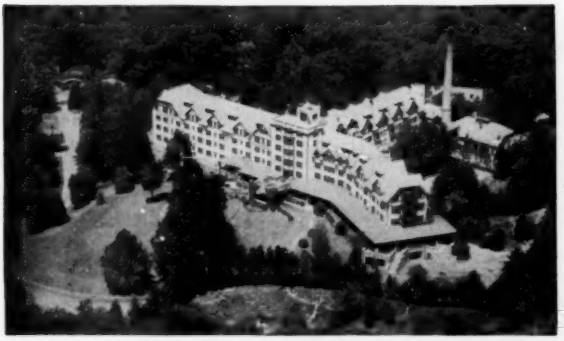

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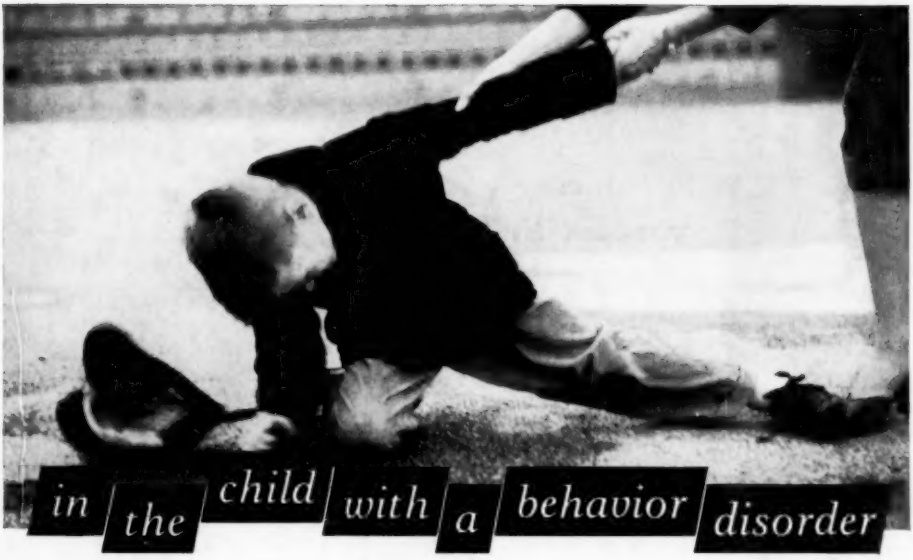

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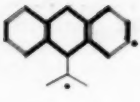

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